ATTACHMENT A

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LAWRENCE LIVERMORE NATIONAL LABORATORY
P.O. Box 808, Livermore, California 94550

LLNL File No.

IL- 9928

LLNL PATENT GROUP

Disclosure and Record of Inventi n

This invention was made in the course of or under prime Contract No. W-7405-ENG-48 between the U.S. Department of Energy and the University of California. This Disclosure and Record of Invention is prepared for the Office of the Assistant General Counsel for Patents, U.S. Department of Energy.

I. Title of Invention:
Integrated Optical Capillary Electrophoresis Chemical Microsensor

Payroll Account No / Department/Division:
9840 J-Division / NAI

II. Inventor(s): (First, Middle, Last)

Inventor(s): (First, Middle, Last)	Title/Position	Employer	Phone No.	Fax No.	Mail Stop
Anthony, J., Ruggiero	Physical Chemist	LLNL	3-1020	2-4544	L-183

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PATENT & TRADEMARK OFFICE

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TC 1700

III. Abstract

This invention is a palm size chemical micro-sensor module that has detection sensitivities in the sub-ppm range and is constructed using a unique combination of integrated optical and planar chip micro-fabrication techniques. A chemical analysis instrument on a chip, this sensor will separate and identify components of complex mixtures using capillary electrophoresis (CE) and a novel universal optical detection system. The detection system is based on two beam interferometry using integrated optical wave guide structures in a Mach-Zehnder interferometer geometry. It can be configured to detect chemical species separated by CE by measurement of either direct refractive index (RI) changes due to the analyte, or photo-induced RI changes resulting from analyte absorption. The latter changes can be either photo-thermal in nature or result from polarizability differences between ground and excited states of the analyte. Designed for minimum size and a low prime power requirement, this device will be suitable for use as an operator controlled field instrument or as an unattended sensor on a wide variety of platforms (e.g., on UAV's or in unattended ground sensor systems).

IV. List past uses, current uses and potential uses for your invention:
LLNL or Government uses or possibilities for use:

Rapid, automated trace chemical analysis and in-situ identification of aqueous effluents, extracts or condensates associated with the development , production or handling of weapons of mass destruction (WMD). Battlefield detection of biological and chemical warfare agents

Commercial, or other uses or possibilities for use:

Applications of this technology include environmental monitoring, forensics science, pharmacological and medical sample analysis and industrial chemical process monitoring.

V. Documents, publications and presentations, describing the invention, that you have published or prepared for publication, or presented on the subject. Also, include presentations and publications planned within one year from now:

Title/Subject	Date	Publication No.
Ultrasensitive Compact Integrated Optic Sensors for Trace Analysis of Complex Aqueous Mixtures, FY[redacted] Advanced Concepts Proposal and Pres.	[redacted] LLNL	
Presentations to DOE NN-20 Officials atLLNL	[redacted]	
	[redacted]	
Optoelectronic Sensors at LLNL., DOD Photonics Conference	[redacted]	
Mclean VA ,		

All presentations and documents to date have been for Official Use Only See attached note

VI. Related Documents, (Including patents, other publications): Pleas include: Patent No.'s, Authors, Title, Publication Date, etc.
none

LLNLPatent Group [redacted]

VII. DESCRIPTION:

Background of the invention, including technical problems addressed by it:

See attached documents. Currently the primary limitation to the widespread use of capillary electrophoresis (CE) for trace field analysis is the lack of suitable low-sample volume (nanoliter-picoliter) optical detectors. Consequently, the high separation resolution delivered by CE is often lost at the detection stage. The most sensitive optical techniques currently in use are based on laser induced fluorescence and are limited to fluorescent molecules or molecules that can be easily derivitized with the appropriate fluorophore.. This limitation often precludes the use of CE for ultrasensitive field deployable sensors. Work on universal CE detectors (detectors that respond to virtually all compounds) is currently a major topic of research. DOE NN-20 Advanced Concepts research in FY[redacted] and FY[redacted] explored the fundamental measurement physics, feasibility and general performance issues involved in the design of a novel all solid state field deployable ultra-sensitive universal CE detector/chemical sensor system . The device is based on two beam interferometry in compact fiber coupled integrated optic (IO) Mach-Zender waveguides. In this type of sensor, the optical phase of the light passing through the device is modulated by a change in absorption induced refractive index in the CE capillary caused by the chemical species to be detected. The phase modulation is then measured interferometrically by comparing the phase of the light in the CE sample arm to the reference arm. The key feature that separates this approach from other thermo-optical and interferometric based CE detection approaches is the use of *close coupled CE/IO device architecture's*. This sensor has a number of attractive features. Optical phase information is demodulated, by detection of all the light emerging from the interferometer rather than a spatially selected component or fringe. Consequently, the signal is independent of thermal lensing artifacts due to the spatial distribution of the excitation beam and is also much less sensitive to misalignment than conventional fringe shift techniques. The system is also well suited to both active and passive homodyne stabilization techniques that would be required for field deployment. Other advantages includ , wide dynamic range, high sensitivity, low overall energy budget and the potential for device multiplexing for decreased analysis time and/or improved species identification. Recently, advances in CE miniaturization have resulted in the development of entire CE systems including electrokinetic sample injectors on palm sized glass "chips". This type of planarized chip technology is ideal for interfacing with IOCE detection systems described above. As a result of the Joule heating accompanying electrophoresis, thermal management is a crucial parameter in determining both efficiency and resolution in CE separations. At LLNL, we have developed and tested a micro-fabrication strategy for electrokinetically injected planarized CE systems on advanced ceramic substrates. Average size of some of the prototype devices allows them to be placed on top of a US quarter. Choice of CE chip substrate material used in microfabrication provides a yet untapped parameter for CE system optimization. Thermal conductivity of the CE chip substrate can easily be increased one to two orders of magnitude over conventional fused silica and glass based systems. Specifically , the use of sapphire, diamond or CVD diamond would be optimal. With regard to an IOCE type detector /sensor system this should translate to increased system response time and decreased analysis time. New CE chip substrate materials also permit optimization of crucial solute/capillary wall interactions via choice of inherent substrate surface charge states.

Summary of the Invention (you may attach a paper). Please include a sketch of the invention, if possible:

See attached documents

PROPRIETARY INFORMATION FOR INTERNAL LLNL USE ONLY

VIII. Inventor's Permanent Home Address(es):

Name	Citizenship	Street Address	City, State, and Zip Code
Anthony J. Ruggiero	USA	1251 Murdell Lane	Livermore, CA 94550

Please attach a separate sheet for additional inventors.

IX. Funding Source or Project Under Which the Invention Arose: Please include subcontracts or special project information.
DOE NN-20 Advanced Concepts Program

Resource Manager: Jim Caselli Phone No.: 422-9055

B&R No.: GC0101093 LLNL Account No.: 5382-50 Subcontract No.: (if applicable)
DOE Program Code: ST043D

Is funding presently being provided for development of your invention: Yes: X No:
Pl ase state the source of funds: (if same as above, please so state)
same as above

Do you reasonably expect future funding from the current source or other sources: Yes: X No:
If yes, what is that source DOE NN-20 Office of Research and Development

X. Conception (Date, Place): [redacted] at LLNL
Conception Date Conception Place

Earliest documentation of your invention: (please provide date and identify the document)

First Sketch or Drawing: [redacted]
First Written Description: [redacted]

Names of witnesses or others with knowledge of facts relating to conception:

Full Name	Organization	Telephone Number
Albert J. Ramponi	LLNL / J-Division/ NAI	423-3363
David H. Dye	LLNL / NAI	422-5036

XI. Reduction to Practice:

Date first model completed: July 1994
Dat of operation and testing: July 1994
Place of test: LLNL
R sults of testing: Demonstrated general feasibility of detection concept

Witnesses or others with direct knowledge of test:

Full Name	Organization	Telephone Number
Albert J. Ramponi	LLNL J-Div / NAI	423-3363
Mike Staggs	LLNL ERD	422-3682

I(We) believe myself(ourselves) to be the first and original inventor(s) of the above-described invention:

INVENTOR: Anthony J. Ruggiero DATE: [redacted]
WITNESS: A. Ramponi DATE: [redacted]
INVENTOR: DATE:
WITNESS: DATE:
INVENTOR: DATE:
WITNESS: DATE:

LLNL File No.: IL- 9928

CLASSIFICATION REVIEW MUST BE COMPLETED FOR ALL UNCLASSIFIED DISCLOSURES

Basis for unclassified release:

X Outside scope of AEA and EO

__ CG-DAR-1, Topic(s) ____

__ Other Guide(s) ____

Topic(s) ____

UCNI: X NO __ YES, guide ____

Authorized Derivative Classifier:

Albert J. Ramponi

Name

J-Division Group Leader

Title

A. Ramponi

Signature

Confirming Reviewer:

Iren Moen

Name

Iren Moen [redacted]

Signature

FOR LLNL PATENT GROUP USE ONLY

Possible Statutory Bars:

Publication:

Public Use/Sale:

Recommended Filing Date Due to Possible Statutory Bars:

READ AND UNDERSTOOD BY:

LLNL PATENT ADVISOR

[redacted]

DATE

TL-9928

[redacted]

Regarding documents, publications and presentations, describing the invention, that you have published or prepared for publication, or presented on the subject. Also, include presentations and publications planned within one year from now:

All presentations, briefings and written documents to date involving this invention have been to DOE NN-20 sponsors or goverment agencies and were for official use only. The following publications/presentations are planned in the immediate future

Mark Lowry and Anthony Ruggiero, "Optoelectronic Sensors at LLNL" ,,DOD Photonics Conference. [redacted]
Mclean VA ,

Anthony Ruggiero and Micheal Staggs , "Laser Beam Coupling to Micro-Capillary Tubes", in preparation for submission to Analytical Chem Lett. in late summer [redacted]

Anthony Ruggiero and Micheal Staggs ,"Universal CE Detection Using Two Beam Interferometry", in preparation for submission to Analytical Chemistry in late summer [redacted]

Advanced Concepts Program

—Ultrasensitive compact integrated optic sensors for trace analysis of complex mixtures —

Principal Investigator: Anthony J. Ruggiero

J-Division
Lawrence Livermore National Laboratory

[redacted]

We are developing a unique field deployable microsensor for trace analysis of aqueous mixtures

the sensor system incorporates:

- micro-analytical chemical separation via Capillary Electrophoresis
- "universal" detection by two beam interferometry using integrated optic technology

target application: trace component analysis of waste water, condensates, and leachates associated with refining, processing and reprocessing of nuclear materials

additional applications:

- analysis of CW and BW agents and associated chemicals
- pharmo-kinetic and metobolic sensors
- industrial chemical and biochemical process control monitoring
- environmental monitoring

Desired microsensor characteristics

high detection sensitivity
large dynamic range
low sample volume requirements
compact, lightweight, rugged, and reliable
low energy budget (power consumption)
rapid automated sample handling and real time analysis
level of automation suitable for unattended operation or RPV

Integrated electro-optical components are well suited to sensor applications

IO components are the optical counterpart to integrated electronics

light signals are controlled and manipulated electronically within miniaturized waveguides made on a common substrate

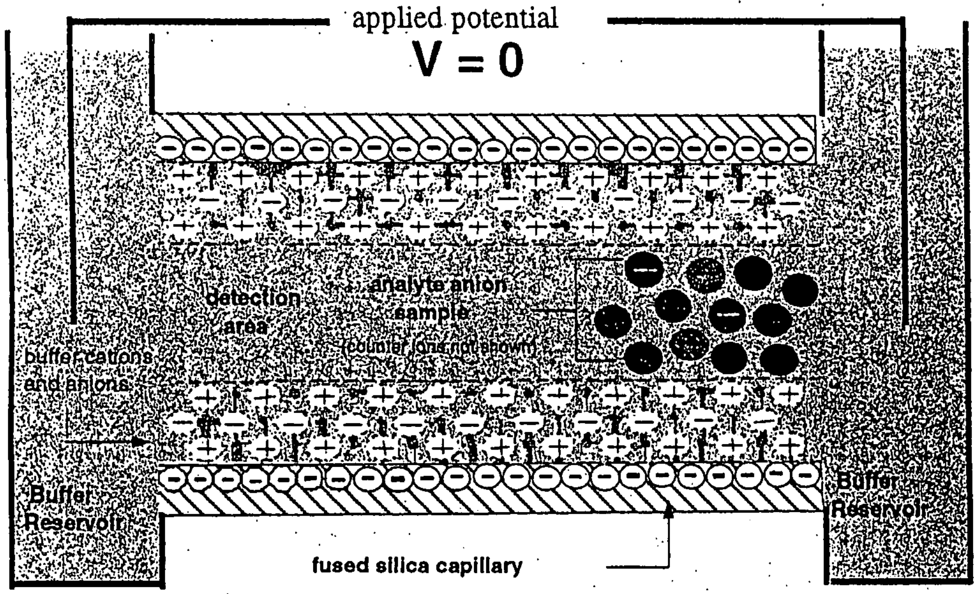
waveguide structures confine, guide and provide a propogation path for the light

- alignment and mechanical sensitivity issues are minimized
  - low optical loss
  - no moving parts involved in beam manipulation and modulation
- low drive voltage requirements
- compact and modular packaging
  - multiple optical components can be combined on a single chip
  - multiple sensor chips can be multiplexed

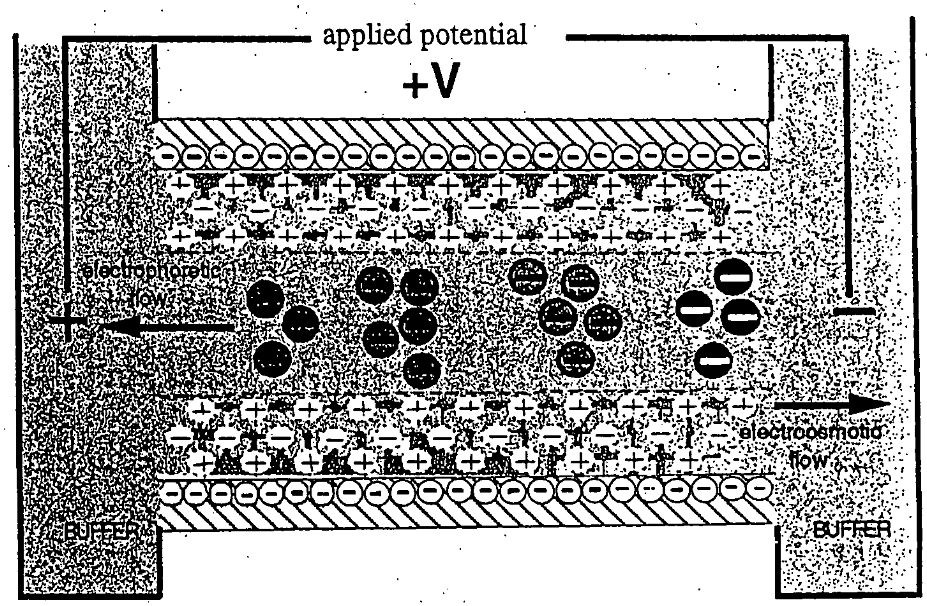
Capillary electrophoresis is a calibrated micro-analytical chromatographic technique

In CE, sample ions in an applied field differentially migrate and are detected at characteristic transit times.

(1) t = 0, sample injected into capillary



(2) t = t1, sample component 1 detected



CE combines the strengths of both HPLC and conventional electrophoresis

capable of operation in aqueous media (most forms of liquid chromotography require non-aqueous solvents)

small sample volumes (nanoliters to picoliters)

resolution is independent of column length

ideal choice for trace analysis of

- inorganic ions, small organic molecules
- organic acids, water soluble polymers
- biomolecules (protiens, peptides, neorotransmitters, DNA etc.

micro-machined CE systems with integrated sample injection have been fabricated on silicon and glass and is currently an area of active research

Widespread use of CE for trace analysis in field deployable sensors is limited by detection technology

suitable low sample volume (nanoliter to picoliter) optical detectors for micro-analytical fluid phase techniques such as CE are an active area of research

laser induced fluorescence is currently the most sensitive optical technique in use

- limited to fluorescent molecules with large quantum yields
- molecules that can be easily derivitized with the appropriate chromophore
- many naturally fluorescent chromophores are quenched in water

Combining CE and integrated optical interferometry offers several advantages for chemical sensing

incorporation of a separation step in a sensor system dramatically reduces selectivity requirements

electric field driven separation based techniques like CE are:

— rapid

— exhibit excellent resolution performance

— well suited to miniaturization, microsampling and automation

optical phase shift measurements are extremely sensative and can be used as "universal" detectors

well developed IO micro-fabrication techniques make possible

— increased on chip functionallity

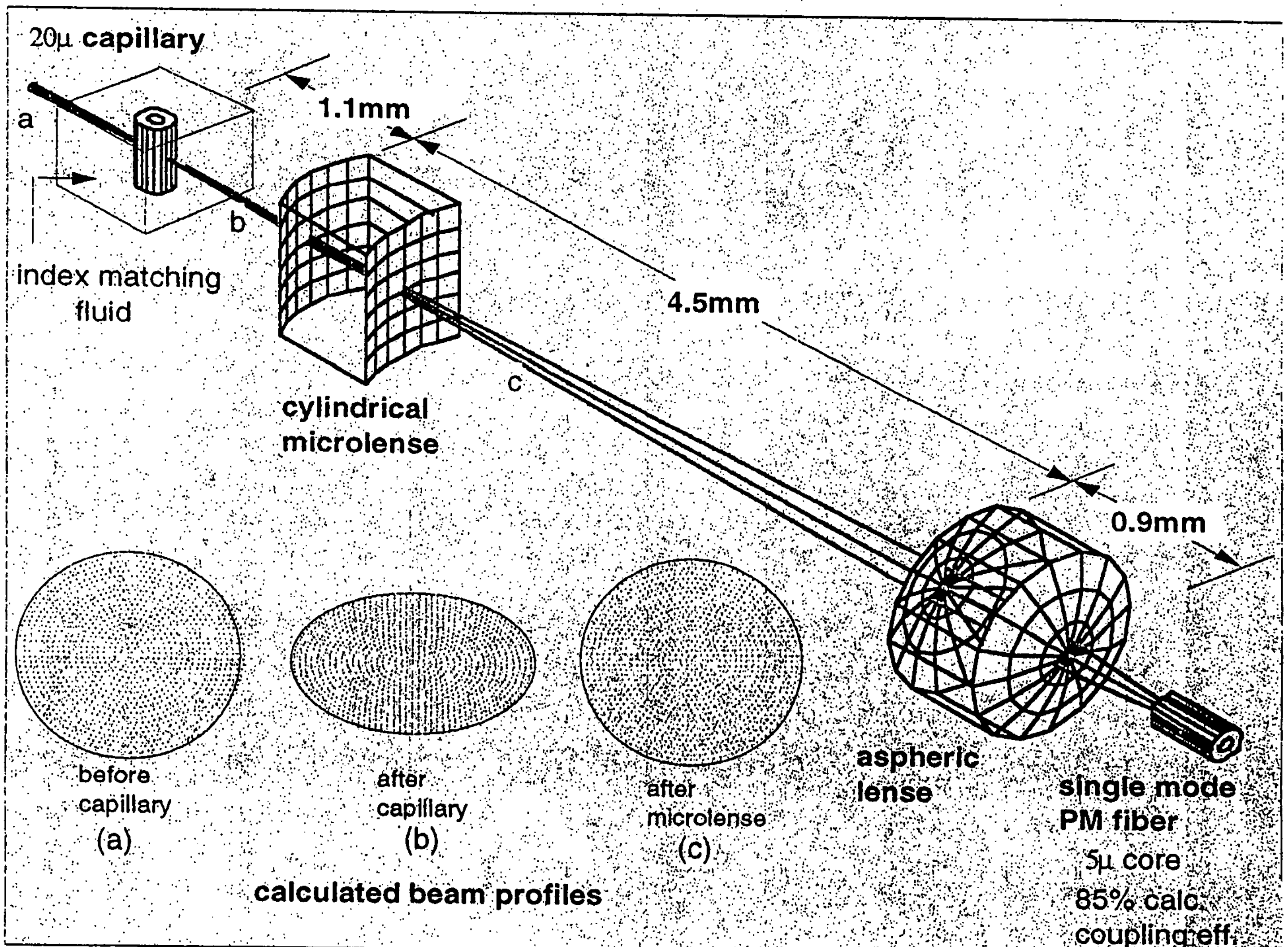
— low power consumption and ease of packaging

IO components are already established as reliable , rugged and field proven

— temperature stable

— impact resistant

Computer modeling was used to design a cylindrical microlense to correct for systematic optical aberations



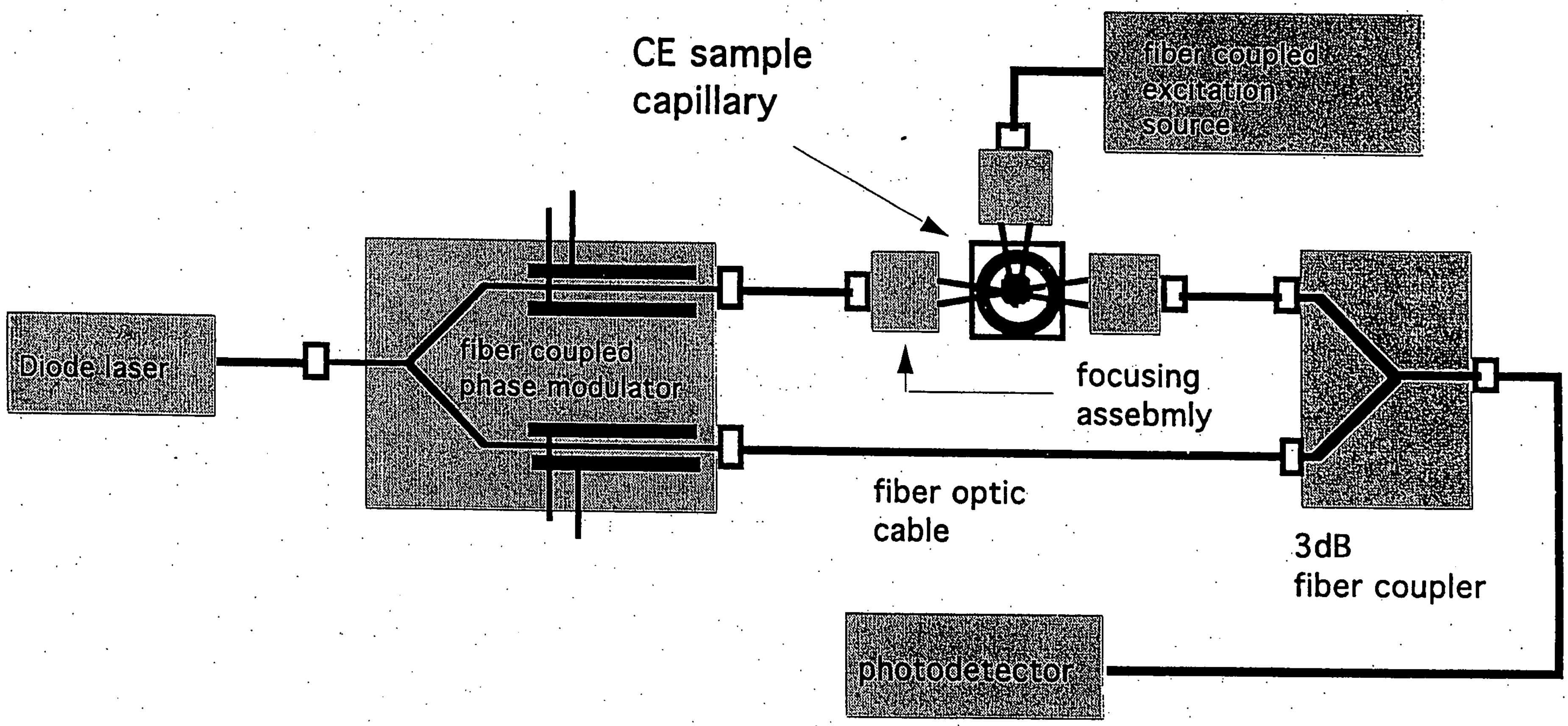
The IOCE sensor can be configured in two detection formats based on optical phase shift measurements

direct refractive index (RI) measurements based on modulation techniques

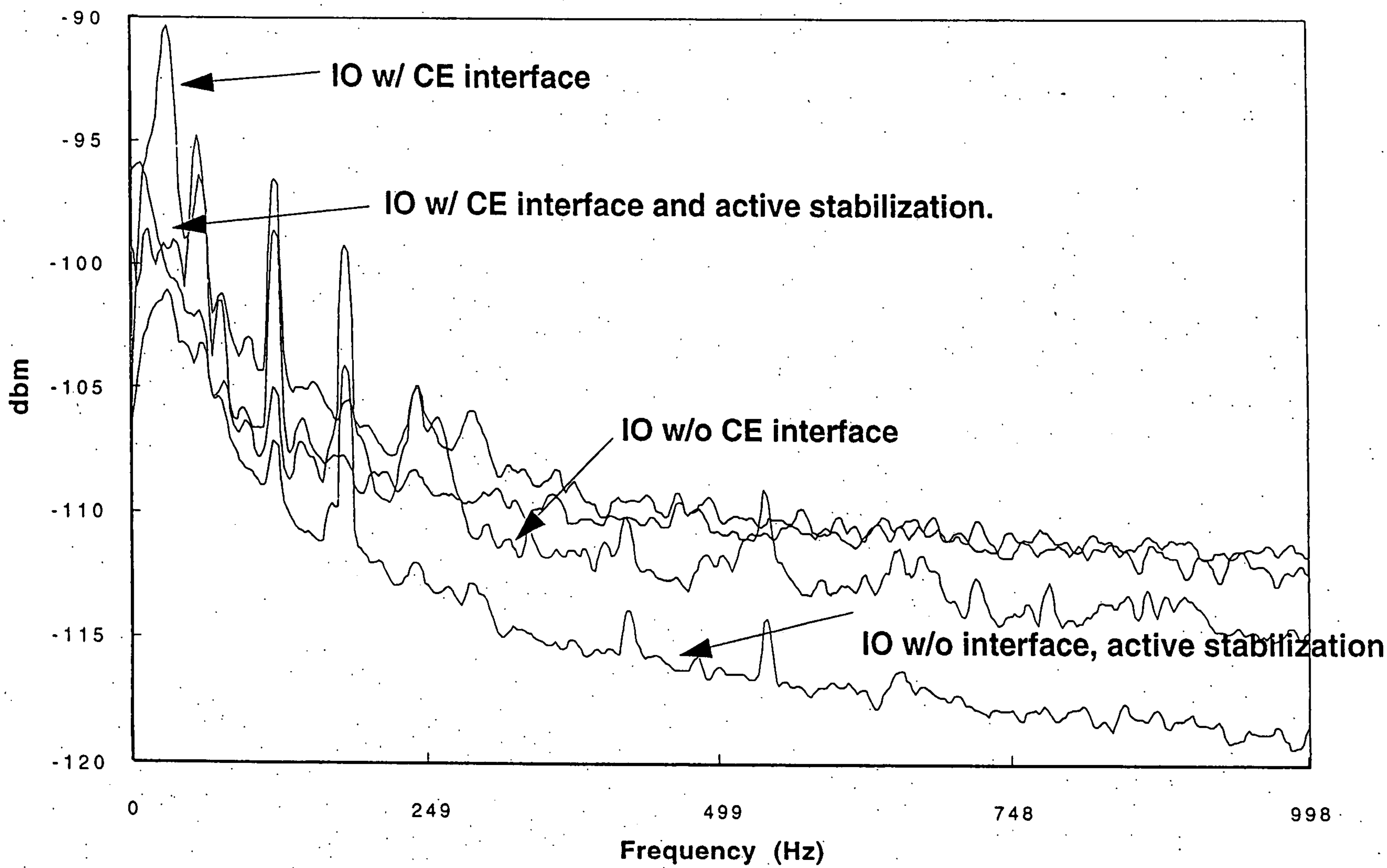
photoinduced RI measurements

- photo-thermal detection
  - absorption by resonant optical excitation induces a refractive index change by local heating of the sample excitation volume
  - the refractive index change is detected by the nonresonant MZ probe beam
- laser induced RI detection * (new technique under development)
  - absorption by resonant optical excitation induces a refractive index change of the sample excitation volume via the excited state polarizability
  - the refractive index change is detected by the nonresonant MZ probe beam

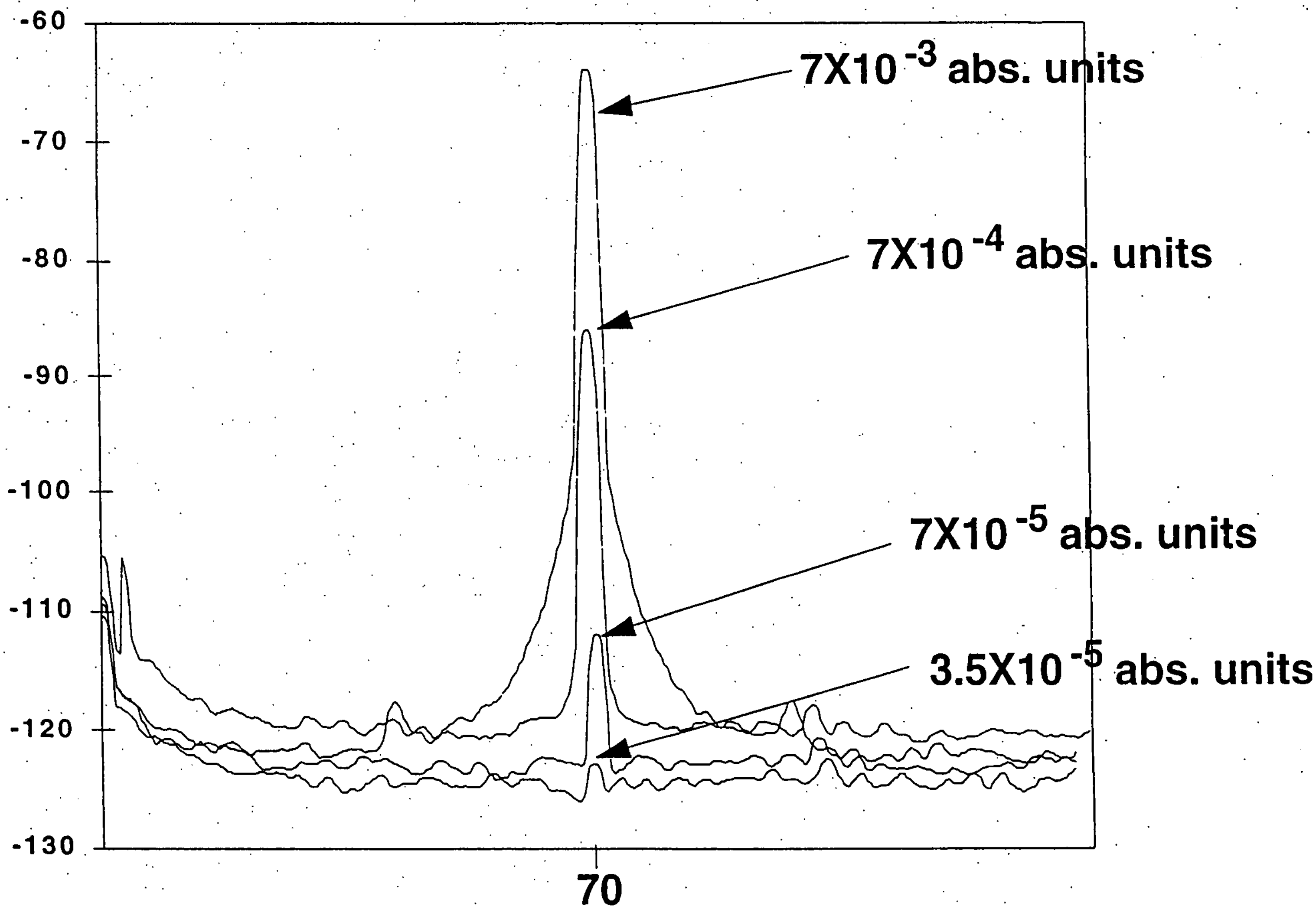
Schematic of discrete component IOCE prototype for Phase I feasibility studies



Spectral noise analysis of the Phase I discrete component system prototype



Signal spectra of thermo-optical absorbance measurements made on fluorescene/water samples



Comparison with competing absorbance detection technologies* for a 20μ pathlength in abs. units

universal detection approaches demonstrated in chromatographic applications include:

- direct absorption - $5X10^{-2}$
- thermal lense detection - $4X10^{-4}$
- Fabry-Perot RI detection - $4X10^{-5}$
- laser intracavity absorption - $5X10^{-5}$
- photoacoustic detection - $1.2X10^{-5}$

theoretical sensitiviy limit for the IOCE approach is calculated to be on the order of $5X10^{-8}$.

Absorbances in the 10^{-5} - 10^{-6} range have been detected with protoype IOCE devices in our laboratory

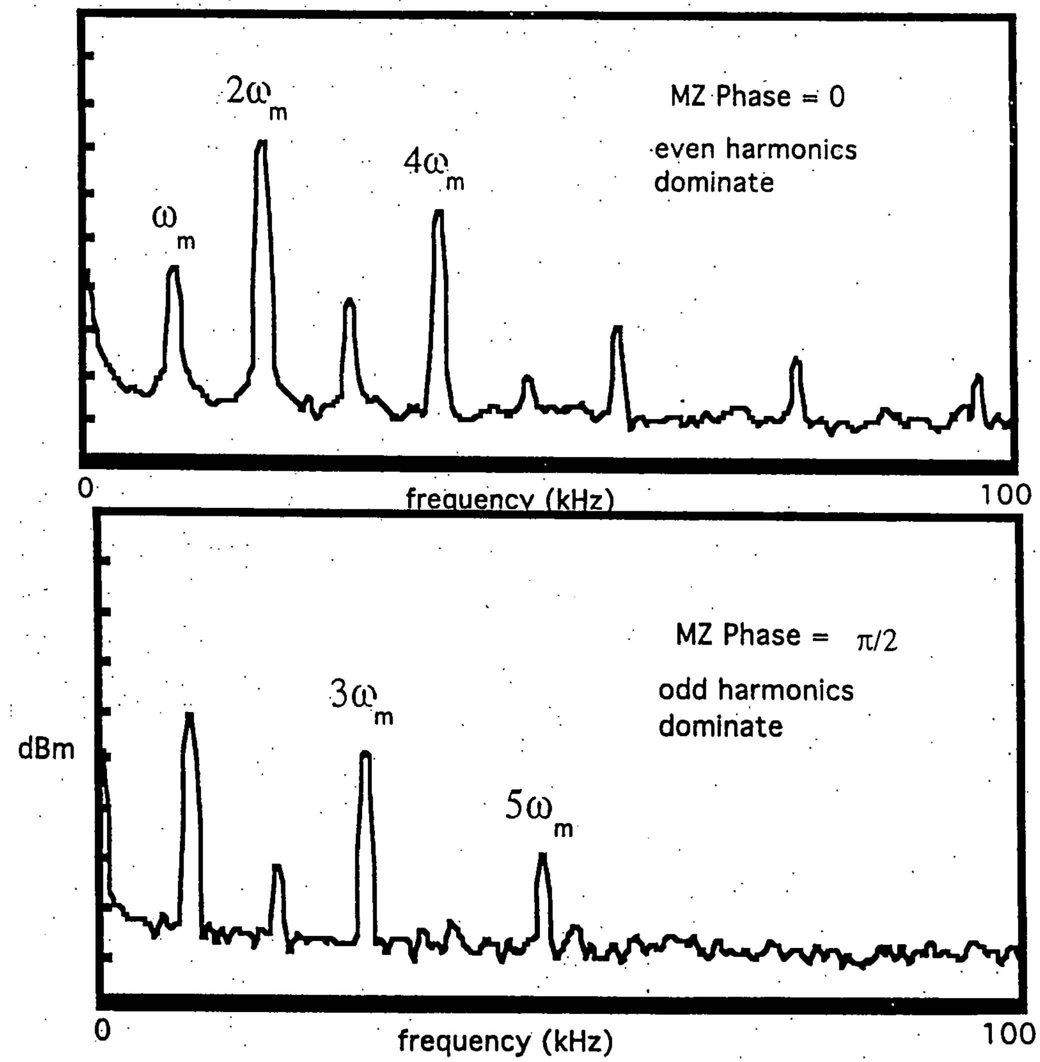
many of the above techniques

- are not easily configured into miniature, rugged fieldable sensors
- general use is restricted by experimental complexity

* adapted from E. Young, "Laser Spectroscopy for Detection in Chromatography" in Analytical Applications of Lasers

Both passive and active techniques are possible for stabilization and improved S/N via phase modulation

signals composed of both in-phase and quadrature components can be generated that eliminate signal fading problems associated with thermal and mechanical drift



Thermal management and surface charge are crucial parameters in determining CE efficiency and resolution

Joule heating accompanying electrophoresis

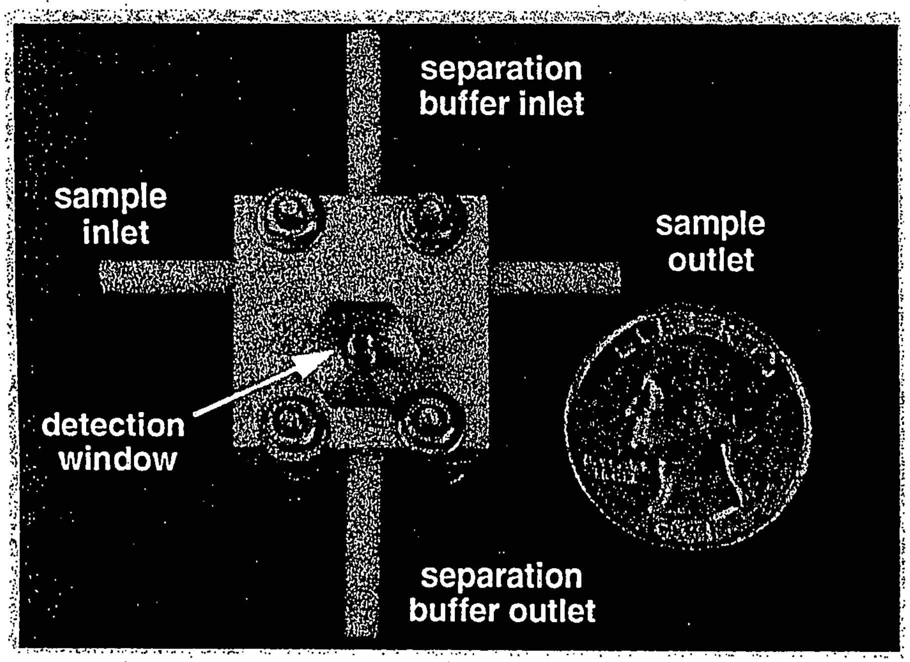
— affects separation resolution

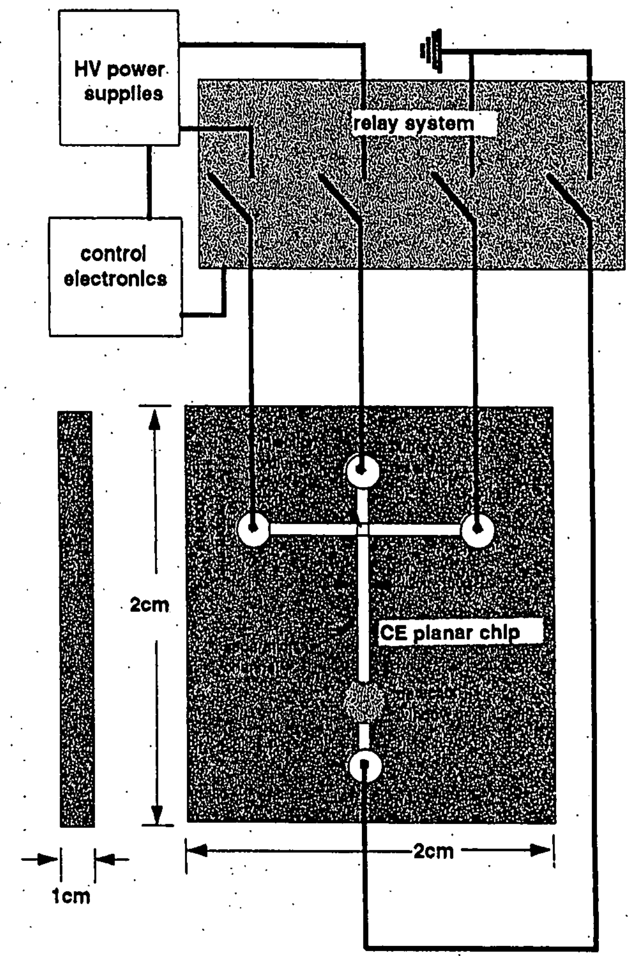
— analysis time by defining operating voltages

surface charge effects separation efficiency through solute wall interactions

the thermodynamics of the system also determins detection response time for thermo-optical based measurements

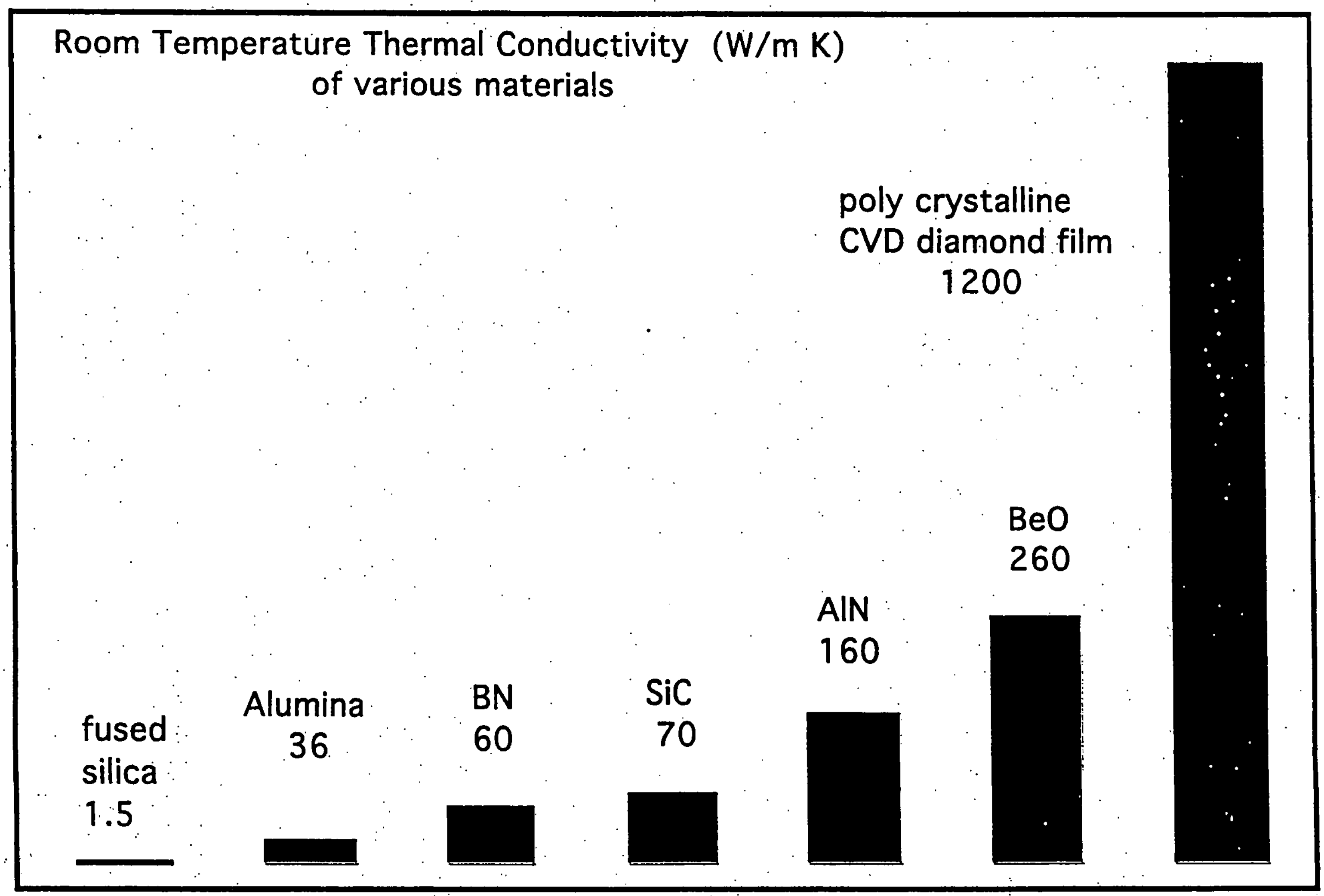
LLNL ceramic planar chip CE prototype with electro-kinetic sample injection





CE system schematic

Choice of CE chip substrate material provides a yet untapped parameter for CE system optimization



Summary

a novel IO based detection scheme suitable for a field deployable sensor has been conceptually developed and initial feasibility has been established

microlense technology has been developed to correct for beam aberations induced at the IO/CE interface, verifying our ability to efficiently couple high quality laser beams from the CE capillary to the IO components

a prototype IOCE device has been fabricated from discrete components and tested

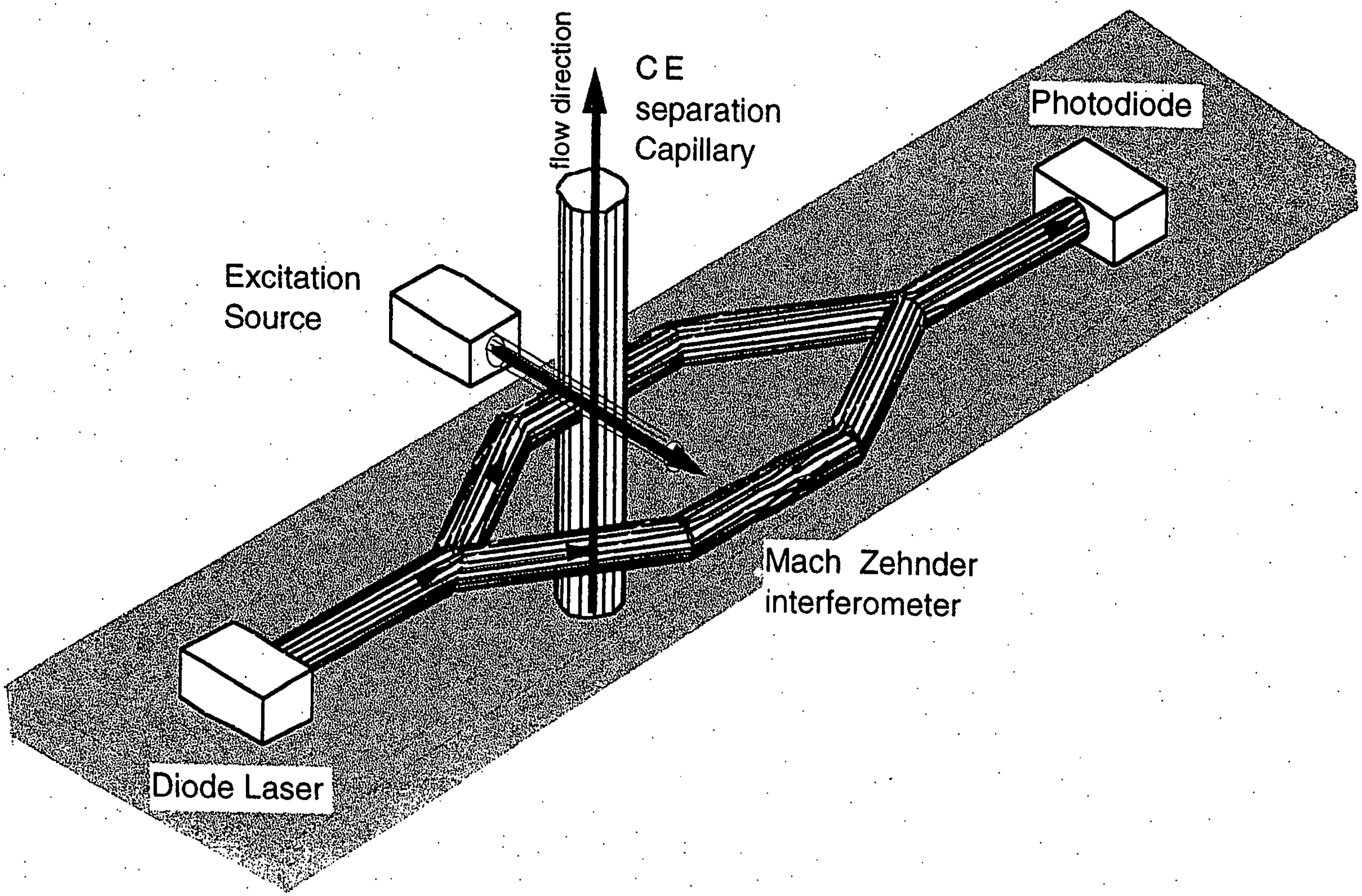
preliminary feasibility tests using active stabilization and phase modulation of the IOCE system have been accomplished

final testing and evaluation of the Phase I demonstration prototype detection sensitivity is currently underway

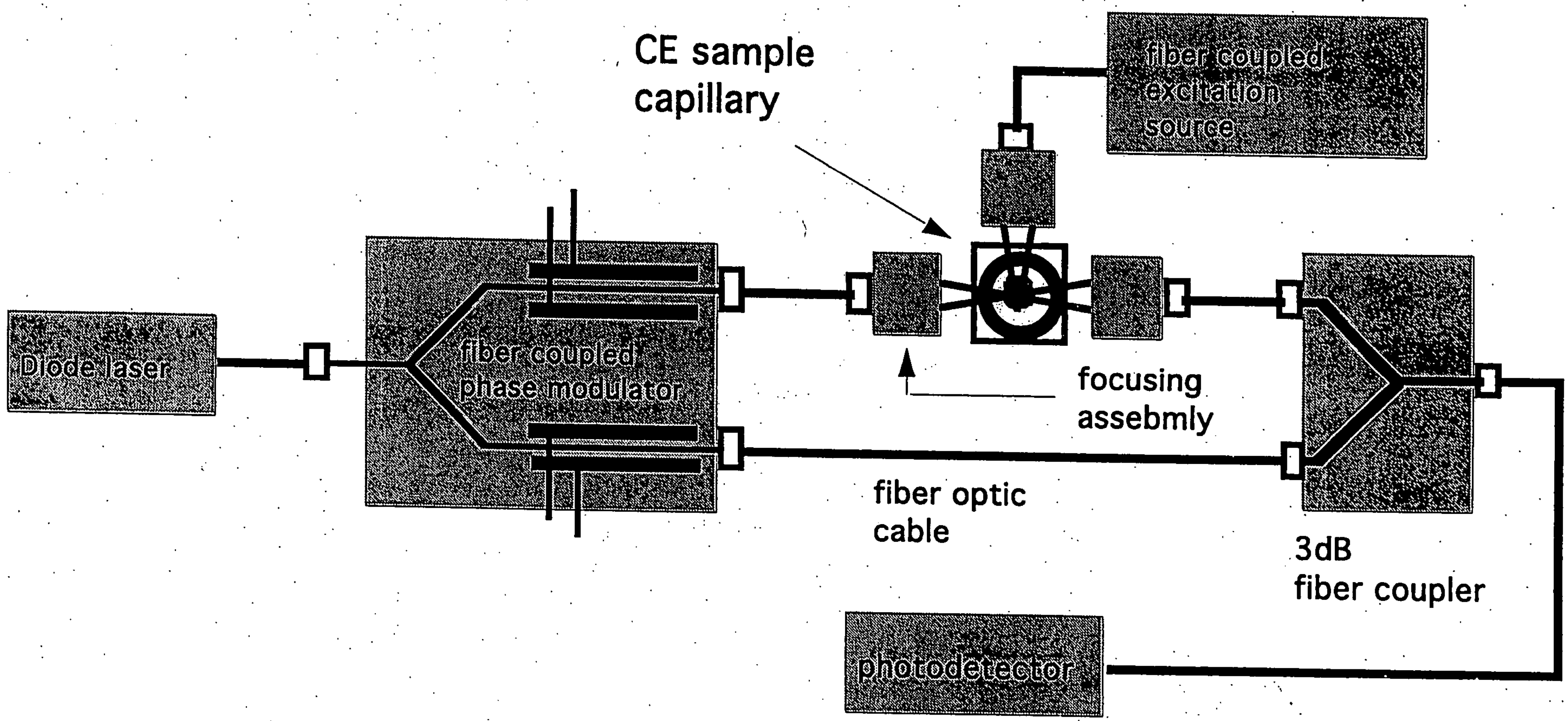
a micro-fabrication strategy for a electro-kinetically injected planarized CE system has been developed and tested

a phase II sensor prototype incorporating IO components with greater on chip functionality and a planar chip CE system has been designed and is under construction

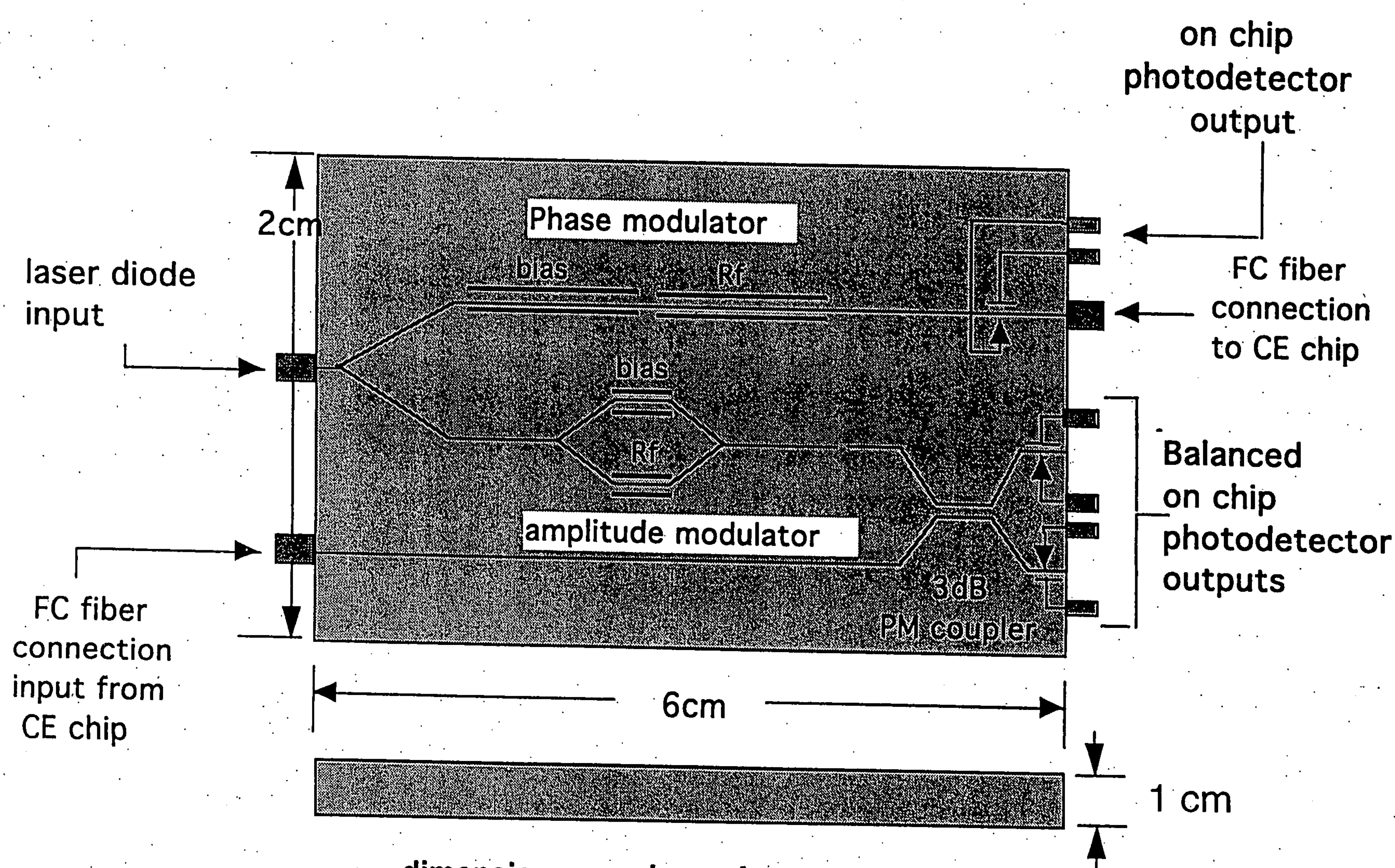
Conceptual diagram of the integrated optic capillary electrophoresis (IOCE) chemical sensor module



Schematic of discrete component IOCE prototype for Phase I feasibility studies

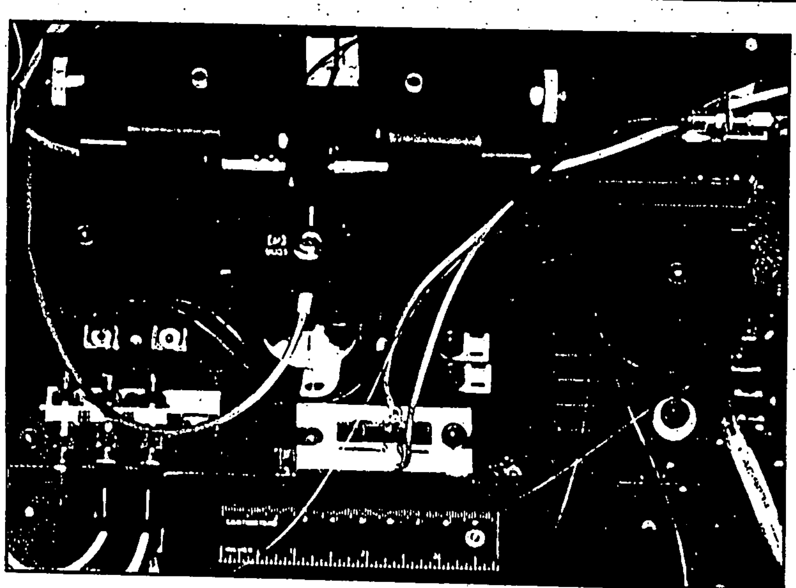


Phase II prototype IO device schematic

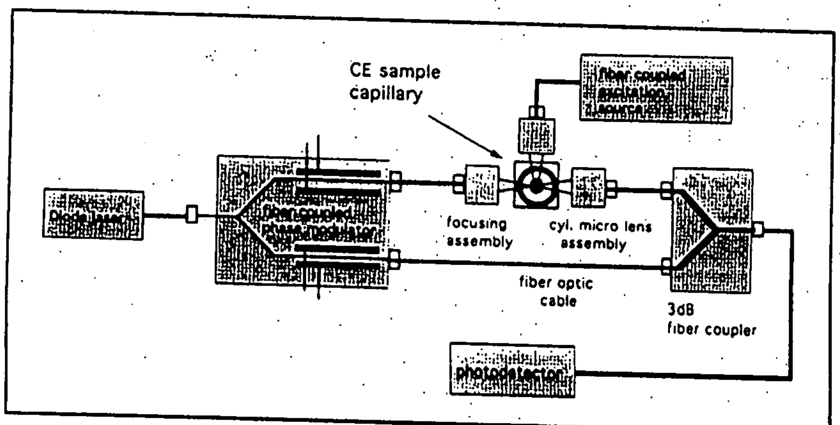


dimensions are shown for connectorized laboratory prototype package

INTEGRATED OPTIC MICROSENSORS FOR TRACE ANALYSIS OF COMPLEX AQUEOUS MIXTURES



Phase 1 discrete component prototype



Schematic of discrete component IOCE prototype

17-T/1124-01

DESCRIPTION:

- Chemical microsensor system employing capillary electrophoresis and unique integrated optic detection technology
- Compact, low energy budget, nanoliter-picoliter sample volumes
- Rapid automated microsampling and real-time analysis

APPLICATION:

- Trace component analysis of waste water, condensates, and leachates associated with refining, processing and reprocessing of nuclear material
- On-site inspections, unattended monitoring or use in remotely piloted vehicles

SPONSOR:
U.S. Department of Energy, NN-20

DEVELOPER:
Lawrence Livermore National Laboratory

INTEGRATED OPTIC CAPILLARY ELECTROPHORESIS MICROSENSOR

FY[redacted]-FY[redacted] LIFECYCLE PLAN PROPOSAL

PRINCIPAL INVESTIGATOR:	**ANTHONY J. RUGGIERO** LLNL, J-DIV. APPLIED TECHNOLOGY PROGRAM, NAI
CO-INVESTIGATOR:	**FRANK PATTERSON** LLNL, PHY. DEP. , PHOTONICS GROUP, PHYSICS AND SPACE TECHNOLOGY
CO-INVESTIGATOR:	**JIM FOLTA** LLNL, MICROTECHNOLOGY CENTER, ELECTRONICS ENGINEERING DIVISION

FUNDING START DATE: [redacted]
FUNDING COMPLETION DATE:

FUNDING

	OPERATING $	CAPITAL $
FY [redacted]	1480K	150K
FY [redacted]	1800K	50K
FY [redacted]	1200K	50K

PROJECT DESCRIPTION:

Based on the results of a recent NN-20 Advanced Concept project, a field deployable chemical microsensor module will be developed for rapid, automated trace analysis and in-situ identification of aqueous effluents, extracts or condensates associated with the development , production or handling of weapons of mass destruction (WMD). The palm size sensor module will have detection sensitivities in the sub-ppm range and will be constructed using a unique combination of integrated optical and planar chip micro-fabrication techniques. A chemical analysis instrument on a chip, this sensor will separate and identify components of complex mixtures using capillary electrophoresis and a novel universal optical detection system.

There are no requirements for volatile, thermally stable compounds or derivitives as in gas chromotography (GC). Aqueous samples containing complex chemical species with a wide polarity range can be analyzed in a single run directly from a crude field sample after a simple filtration. Unlike most forms of high performance liquid chromatography (HPLC) that share this advantage, however, large volumes of non-aqueous solvents are not required. Designed for minimum size and a low prime power requirement, this device will be suitable for use as an operator controlled field instrument or as an unattended sensor on a wide variety of platforms (e.g., on UAV's or in unattended ground sensor systems). It will represent the state of the art in fieldable chemical micro-analytical instrumentation.

PROJECT SUPPORTS:

Treaty on the Non-Proliferation of Nuclear Weapons, Chemical Weapons Convention

PROJECT STATEMENT OF WORK

Objective:

The primary project objective is to develop a compact fieldable micro-sensor module that can be used to rapidly isolate, identify, and quantify inorganic or organic cations and anions of interest in water samples, condensates, leachates, or aqueous atmospheric aerosol extracts. The module will be a compact, energy efficient device that can be easily incorporated into a variety of field platforms. It will include a versatile micro-fabricated pre-analysis sample preparation and injection manifold that will enable the system to be easily interfaced to user specified sample collection formats.

Application:

After calibration for the chemical species of interest, the field deployed system will detect and quantify radionuclides and chemical signatures in aqueous effluent samples obtained from facilities that are potentially indicative of weapons of mass destruction (WMD) proliferation activities. Dual use and spin-off applications of this technology include environmental monitoring, forensics science and, pharmacological and medical sample analysis.

Prior Work:

The proposed work is a continuation of a DOE NN-20 Advanced Concept project initiated in FY[redacted] by the P.I. to investigate the feasibility of combining solid state laser and integrated optic (IO) component technology with micromachined planar chip capillary electrophoresis (CE) systems. Prior work emphasized fundamental physics of the IOCE interface and the detection technology, providing optical and thermo-mechanical design tolerances for the system.

Capillary electrophoresis (CE) has been regarded by many in recent years as a major breakthrough in fluid phase separation science.[1] It is now an established and well understood microanalytical technique. CE combines the strengths of both high performance liquid chromatography (HPLC) and conventional electrophoresis to yield rapid, precise, automated, and highly efficient analysis of complex chemical mixtures using minimal injected sample volumes (picoliter-nanoliter, see Figure 1.). Most forms of high performance liquid chromatography require non-aqueous solvents, CE, however, is capable of operation in aqueous media, making it the ideal choice for trace analysis of inorganic ions, small organic molecules, organic acids, water soluble polymers and biomolecules (proteins, peptides, neorotransmitters, DNA etc.). Samples for analysis can be obtained directly in the fluid phase, or as extracts from solids or condensates. Analyte concentration on solid phase chemical or particle filters prior to aqueous extraction and analysis is also possible.

The rapid growth of this analytical technique is due to the inherent simplicity of the required hardware and the fact that the physics of the separation are easily controlled by the choice of electrolyte. In essence, the electrolyte and polarity of the applied voltage programs the capillary to separate anionic, cationic, or neutral species. This is in contrast to established ion analysis techniques, such as ion chromatography, where separations are wholly dependent on dedicated specialized analytical columns. High CE separation efficiencies result from the use of small separation channels or capillaries, 20-100 microns in diameter. Since the efficiency is independent of channel length, the entire approach is extremely amenable to micro-fabrication and miniaturization. In fact, CE performance improves with reduced size.

Chemical sensing systems based on capillary electrophoresis can be *versatile, sensitive and selective*. The detector can be optimized for sensitivity without regard to selectivity, while the electrophoresis separation capillary can be optimized to yield high selectivity toward a particular chemical species or class of chemicals. The system is versatile in the sense that the same system hardware can be used for analysis of a wide variety of different types of chemicals by manipulation of the CE separation conditions. This is in contrast to most chemical sensors in which a tradeoff exists between versatile performance, sensitivity and selectivity.

CE based sensors, with their ability to directly analyze crude aqueous field samples, can offer tremendous advantages in the treaty verification and proliferation detection arenas. For example, identification of precursors and degradation products of chemical warfare agents must often be unambiguously identified from various matrices during the treaty verification process. The degradation (hydrolysis) products, alkyl-substituted organophoshorus acids, are polar, have low volatility and are easily isolated from various matrices by extraction with water. While easily analyzed using CE, these compounds are difficult to identify directly using other analytical techniques, such as gas chromatography (GC), in which chemical derivitization would be required.

Currently the primary limitation to the widespread use of CE for trace analysis is the lack of suitable low-sample volume (nanoliter-picoliter) optical detectors. Consequently, the high separation resolution delivered by CE is often lost at the detection stage. The most sensitive optical techniques currently in use are based on laser induced fluorescence and are limited to fluorescent molecules or molecules that can be easily derivitized with the appropriate fluorophore. This limitation often precludes the use of CE for rapid ultrasensitive *field deployable* sensors. Notably, laser induced fluorescence cannot be directly applied, in general, to trace analysis of actinides in aqueous solution due to their low fluorescence quantum yields. In addition, radionuclide counting techniques are limited in this application due to the dependence of the detection limit on the observation time and radionuclide lifetime. In capillary electrophoresis, typical peak widths are only several seconds wide and so only a several second observation time is possible without limiting separation efficiency or increasing the total analysis time. Scintillation detectors consequently are not easily optimized for both maximum analysis speed and sensitivity.

Work on universal CE detectors (i.e. detectors that respond to virtually all compounds) is currently a major topic of research. Under Advanced Concepts research in FY[redacted] we explored the fundamental measurement physics, feasibility and general performance issues involved in the design of a novel all solid state ultra-sensitive universal CE detector. As illustrated in Figure 2., the device is based on two beam interferometry in a compact fiber coupled integrated optic Mach-Zehnder interferometer (MZI). One arm of the interferometer includes a small section of the CE capillary. Detection of the electrophoretically separated analyte is accomplished by monitoring the optical phase shift that results from refractive index changes in the CE capillary as different chemical species pass through the MZI sample arm. A substantial increase in sensitivity is obtained by including an amplitude modulated excitation beam to generate photo-induced refractive index changes via analyte absorption. Phase modulation resulting from the absorption process is detected by optical heterodyning with the MZI reference arm. Excitation

wavelengths can be chosen to enhance the selectivity of specific analytes or to provide a universal detection capability. Most aqueous solutes have strong broadband absorptions in the UV spectral region.

The key feature that separates this approach from other thermo-optical and interferometric-based CE detection approaches is the use of close coupled CE/IO device architectures and all solid state laser technology. This approach has a number of attractive features. Optical phase information is demodulated, by detection of all the light emerging from the interferometer rather than a spatially selected component or fringe. Consequently, the signal is independent of thermal lensing artifacts due to the spatial distribution of the excitation beam and is also much less sensitive to misalignment than conventional fringe shift techniques. Unlike, photothermal lens (PL) and photothermal deflection (PD) based detection systems, the signal level is not dependent on the distance between the sample and the photodetector. PD and PL techniques typically require sample to detector distances on the order of 1.5m - 0.15m for maximum sensitivity, the integrated optic capillary electrophoresis (IOCE) system, however, is inherently compact with no large optical lever arms and subsequent mechanical stability requirements.

The system is also well suited to both active or passive homodyne stabilization techniques that would be necessary for actual field deployment, as well as programmable multiple modulation based detection schemes for removal of background absorptions. Other potential advantages include, wide dynamic range, high sensitivity, and low overall energy budget. Results from our FY[redacted] Advanced Concepts effort have established the general feasibility of this approach by: (1) demonstrating our ability to efficiently couple high quality optical beams between buffer filled CE capillaries and waveguide structures, (2) developing an actively stabilized discrete component IOCE system protoype, and (3) demonstrating detection of photo-induced absorption signals in 20 micron water filled fused silica capillaries at detection levels on the order of $2X10^{-7}$ absorbance units.

In the last few years, advances in CE miniaturization have resulted in the development of entire CE systems including electrokinetic sample injectors on palm sized glass "chips".[2,3] This type of planarized chip technology is ideal for interfacing with IOCE detection systems described above. As a result of the Joule heating accompanying electrophoresis, thermal management is a crucial parameter in determining both efficiency and resolution in CE separations. To address this issue, we have developed and tested a micro-fabrication strategy for electrokinetically injected planarized CE systems on advanced high thermal conductivity, nonconductive ceramic substrates. (see Figures 3 and 4.) Although these devices are more difficult to fabricate than the conventional glass packages they promise substantially higher performance. Average size of some of the prototype devices allows them to be placed on top of a US quarter.

Choice of CE chip substrate material used in microfabrication provides a yet untapped parameter for CE system optimization. Thermal conductivity of the CE chip substrate can easily be increased one to two orders of magnitude over conventional fused silica and glass based systems. For an IOCE-type detector system this should translate to increased system response time and decreased analysis time. New CE chip substrate materials also permit optimization of crucial solute/capillary wall interactions via choice of inherent substrate surface charge states. The final phase of our IOCE Advanced Concepts work for FY[redacted] will further develop and characterize the IOCE detection technology and integrate it with the ceramic planar chip CE devices into a full phase II prototype sensor. This phase II prototype will provide the relevant design criteria and engineering tolerances for the sensor module proposed here.

Collaborators: Initial collaborations will be concerned with optimizing the planar chip CE system performance, automated sample preparation and dual use applications. Possible collaborators include CE researchers, Dr. Richard Chadwick (Analytical Chemistry R&D Division, Alergan Optical), Professor Warner Kuhr (UC Riverside), Dr

T.R. Wang (Applied Research and Advanced Development Division, Beckman Instruments). As the IOCE technology reaches maturity and is ready for final testing, collaborations with researchers at LLNL and other DOE laboratories that have been involved in identifying proliferation signatures found in aqueous effluents and/or developing chemical analysis protocols for these signatures based on CE is anticipated.

Work for others: None

Proposed Work and Scientific Basis:

We propose the final design, fabrication and testing of a complete chemical micro-sensor module including automated micro-sample injection and prefiltering systems. The sensor system will be based on planar chip capillary electrophoresis, integrated optical detection technology and micro-electro-mechanical sample processing. Using the physical insights and engineering data obtained from our FY[redacted] IOCE Advanced Concepts studies, an optimized IOCE sensor module will be developed. Previous Advanced Concepts Phase I and Phase II IOCE sensor prototypes have been designed around commercially available laser and IO components without regard for the minimum obtainable package size or overall system energy efficiency, since the intent of that work was initial demonstration of laboratory feasibility and engineering development. The work proposed here will determine the limits of microfabrication technology and packaging for this type of device and address packaging concerns pertinent to higher levels of subsystem integration. The project will proceed in three phases, (I) baseline, risk reduction, testing and development of enabling microtechnologies, (II) initial sub-system integration and testing, and (III) final microsensor module fabrication and performance demonstrations. The FY[redacted] effort will be composed of four parallel efforts: high performance substrate planar chip CE design, optimization and testing, fiber coupled UV microchip laser source development, monolithic (single substrate) integrated MZI/laser/ photodetector IO chip fabrication, and prototyping of a microvalve sampling and injection manifold. FY[redacted] will comprise final subsystem integration, system electronics packaging and performance testing of the completed chemical microsensor module under simulated field conditions. IOCE microsensor technology makes simultaneous operation of multiple sensor modules either discretely packaged and interfaced or fabricated on a single chip feasible. Advantages and potential applications of this type of multiplexed sensor operation other than simple system redundancy will also be evaluated.

Integrated optical components of the type required for the sensor module and used in our Advanced Concepts prototypes were based on lithium niobate waveguide technology. This IO technology is well established as reliable, rugged and field proven both in military and industrial applications. Hybrid microintegration of laser diodes and photodetectors with these components has been reported and is a viable option for use in the proposed sensor.[4,5] The technology for lithium niobate IO fabrication and packaging is well established at LLNL. Use of lithium niobate for the waveguide material, however, precludes the possibility of monolithic integration of the semiconductor laser diode source and semiconductor photodetectors onto a single common substrate. Monolithic component integration can have tremendous benefits for the proposed sensor in terms of absolute package size, reduced coupling losses, enhanced stability and mass production.

We propose to fabricate a fully monolithic integrated sensor detection system on a common GaAs substrate using AlGaAs/GaAs epitaxial growth technology.[6,7] (See Figure 5.) The Mach-Zehnder functionality will be achieved through the use of semiconductor optical amplifiers (SOAs) as optical phase shift elements and amplitude controllers.[8] The ability to utilize the same semiconductor layers for different functionality

dramatically simplifies the fabrication of the laser/MZI/detector chip. Dozens of devices may be simultaneously fabricated in a single production sequence on a 50 or 65mm wafer.

To produce the chip, a laser diode section is defined by forward biasing a (single-mode) waveguide section with parallel optical facets, an SOA is fabricated similarly but with low reflectivity facet interfaces and the photodetector is an unbiased or reverse biased waveguide absorber which generates a photocurrent. The waveguide sections are regrown after etching (photolithographically defined) with transparent, low loss material deposition. Two key fabrication technologies are essential to constructing the SOA MZI chip: chemical etching for definition of laser facets and the low-loss waveguide deposition process for the AlGaAs/GaAs material system. Final package size of a chip based on this technology would be on the order of 1mm x 5mm. We believe that LLNL is uniquely positioned to prototype the MZI sensor chip because the LLNL passive waveguide process on ALGaAs/GaAs is unique in the world and our etching technology is the state of the art. (see figures 6 and 7).

Recent breakthroughs in semiconductor diode laser technology, high efficiency diode laser fiber coupling (90%) and quasi-phasematched frequency conversion technologies make fabrication of a highly efficient, versatile all solid state UV microchip laser excitation source for the proposed IOCE module feasible. Microchip lasers are miniature, high performance solid state diode pumped lasers fabricated from 1-3mm^3 solid state laser "chips". (See Figure 8.) The laser resonator is formed by depositing cavity mirrors directly on the chip faces to form a monolithic cavity. The performance characteristics of these devices result from their inherently short cavity length and pump source induced thermal lensing properties that produce an auto-stabilized condition for efficient single transverse mode (TEM_{00}) operation in conjunction with the marginally flat /flat solid state optical resonator structure. Some of their characteristics include simple single frequency operation, tunability over the gain bandwidth without mode hopping, short pulse and high peak power capability and high speed frequency and amplitude modulation capability. Composite cavity lasers composed of laser "chips" and "chips" of nonlinear materials sandwiched together allow highly efficient frequency conversion of the solid state laser output. Optical design, fabrication and development of suitable fiber coupled UV micro-laser system for the chemical sensor module will be undertaken. Initially, commercially available micro-chip laser modules operating at their fundamental or second harmonic will be used to evaluate this technology and determine the optimal nonlinear frequency mixing scheme for UV generation via sum frequency mixing or third harmonic generation.

Lastly, microfabrication techniques will be used to construct the necessary miniaturized valves and flow capillaries required for the sample collection, pre-analysis processing and injection manifold. Recent advances in the adaptation of microfabrication techniques originally developed for the microelectronics industry have been increasingly adapted to build mechanical devices in the growing field of Micro-Electro-Mechanical Systems (MEMS). Advances in MEMS technology are rapidly increasing the feasibility of integrated microflow systems and micro-instrumentation. The ability to integrate smart microelectronics for instrument control and data analysis along with mechanical and optical components required for a given analytical technique will permit the user to interface with the instrument at a much higher functional level than with present instruments, which are composed of many separate modules that must be interfaced and operated by the user. LLNL has advanced capabilities and experience necessary to develop the proposed components and is already developing a variety of chemical analysis microinstruments with MEMS technology.

We propose to develop a miniaturized sample collection and precision injection system based on micro-valve technology for the capillary electrophoresis chemical analysis sensor module. LLNL and Redwood MicroSystems, Inc. (Menlo Park, CA) are presently working together to expand Redwood's Fluistor™ product line of micro-fabricated valves.

(see Figures 9 and 10) The devices are micro-fabricated in silicon and are based on Redwood's thermopneumatic actuation principle. The microactuator is among the few which provides both high force and displacement needed for valve applications. The actuator motion is precise enough that it can effectively control flows over six orders of magnitude. Efforts are currently focused on new generations of valves which are faster, chemically resistant, normally-closed, and compatible with liquids. Work is also underway to integrate micro-valve arrays with microflow channels, pressure and flow sensors to form high performance, microflow systems for pressure regulation and flow control. We plan to exploit these technological developments in the proposed IOCE chemical sensor module. An important decision for the first prototype is to determine whether to actuate the microvalves with an integrated microfabricated actuator or an external actuator. The integrated microvalve actuator would have size advantages and be more faithful to the "microinstrument" concept, but the external actuator would initially have lower development costs, shorter development times, and possible performance advantages. Consequently, we will develop the first prototypes with external valve actuation in order to demonstrate system performance and then add integrated actuation as we approach final subsystem integration in FY[redacted] Size of the completed microvalve manifold package will be on the order 50x50x3mm. Future generations could be reduced in size to 25x25x3mm.

The proposed microvalve work will leverage the results of ongoing microinstrumentation projects in the LLNL MicroTechnology Center (MTC) such as: (1) microvalve development in a CRADA partnership with Redwood MicroSystems, the world's leader in microfabricated valve technology; (2) development of high-throughput, high resolution capillary gel electrophoresis instruments for DNA sequencing; (3) portable gas chromatography chemical analysis systems; (4) microfabricated chemical reactors for the polymerase chain reaction (PCR); (5) miniature flow cytometers for cell sorting; (6) microchannel coolers for high power laser diode arrays; and (7) microfabrication of precision capillaries by etching and bonding of glass and silicon wafers.

Research and Development Issues:

Issue 1. The planar chip CE technology must be optimized for field sensor applications. CE chip design parameters must be engineered to optimize separation performance and minimum size. The best choice of CE chip substrate material, capillary size, separation voltage, electrokinetic sample injection parameters, and the mechanical packaging of the buffer and sample reservoir feeds must be determined.

Issue 2 An IOCE module package suitable for field deployment that minimizes microphonics and thermal management problems must be designed. A microoptic packaging strategy and optical design for interfacing the planar CE chip, the microchip laser excitation source and the integrated optic detection system waveguides must be developed.

Issue 3 General feasibility of the monolithic single substrate SOA Mach-Zender interferometer concept must be demonstrated at a level of performance suitable for use in the IOCE sensor module. If this approach does not meet expectations, a microoptical packaging strategy for the lithium niobate waveguide devices will need to be developed and implemented.

Issue 5 A compact energy efficient , reliable UV microlaser excitation system suitable for field operation must be designed and demonstrated. An efficient, low power, nonlinear optical frequency conversion scheme based on either third harmonic generation or sum frequency mixing of the micochip laser output must be designed and optimized and packaged.

Issue 6. Design and engineering of an automatic sample collection and prefiltering system must be completed to accommodate true field samples

Issue 7. Size reduction and packaging of support electronics and system power supply must be addressed

Issue 8. The optimum detection format and operating parameters for field deployment must be determined for the IOCE module

During FY97 the following tasks will be performed:

Task 1 Baseline CE and IO micro-package engineering, integration and testing ($500K)

(1.0) detailed mechanical and optical system design
(1.1) microfabrication and evaluation of planar chip CE test components from high performance substrate materials
(1.2) thermo-mechanical characterization and integration of planar chip CE and discrete commercial lithium niobate IO components.
(1.3) preliminary characterization and demonstration of baseline system separation and detection capabilities using optimized CE chip substrates
(1.4) development of IOCE test platfom for sub-system test and evaluation

Task 2 Development and testing of compact, energy efficient, high beam quality UV microchip laser system and interface to IOCE sensor module ($250K)

Task 3 Evaluation and testing of the SOA MZI concept for sensor applications; build and test and characterize a hybrid SOA MZI using discrete components. ($350K)

3.1) Fiber pigtail and package existing LLNL laser diode and SOA chips with polarization maintaining fiber.
(3.2) Test individual components -- SOA gain and phase shift as a funtion of current, laser diode threshold and output power versus current, laser diode linewidth and laser diode susceptibility to optical feedback, polarization extinction ratios of fiber splitters.
(3.3) Configure LLNL laser diode, SOA, photodiode and fiber splitter components into the MZI configuration. Characterize contrast ratio, stability to temperature, vibration and optical feedback effects on MZI transmission.
(3.4) Test and evaluate discrete component prototype developed in task 4.3 in IOCE sensor test system to compare with lithium niobate IO technology.

Task 4 Preliminary design, development and testing of automated microvalve sampling and filtering system. ($380K)

(4.1) Discrete valve development:
Determine actuation mechanism and general approach
Design discrete valve and package (2 iterations)
Photomask layout (2 iterations)
Microfabricate valve chip (2 iterations)
Fabricate package (2 iterations)

Test discrete valves (2 iterations)

(4.2) Sample injection and processing manifold development:
- Design injection manifold chip (2 iterations)
- Design manifold package and interface (2 iterations)
- Solve gas generation/bubble problem
- Photomask layout (2 iterations)
- Microfabricate manifold chip (2 iterations)
- Fabricate packages and interfaces (2 iterations)
- Test manifolds (2 iterations)

(4.3) Discrete copmonent integration and testing with IOCE system

FY[redacted] CAPITAL $ JUSTIFICATION

commercial laser systems for prototype development and testing (customized diode laser and microchip laser systems)	30K
subsystem IO components	55K
micro-manipulation equipment	20K
support electronics and electronic test equipment	45K
Total:	$150K

FY[redacted] SCHEDULED MILESTONES

NUMBER	DUE DATE	COMPLETION DATE
1	[redacted]	

Initial optical and mechanical design work complete. Specification and procurement of critical system components and fabrication contracts complete. Fiber pigtail packaging and fabrication of SOA test chips complete. Preliminary design discrete microvalve system complete

2.	[redacted]	

Fabrication and testing of CE hardware test chips and fixtures incorporating initial design ideas complete. Preliminary evaluation of microchip laser technology and preliminary frequency conversion experiments completed. Individual SOA component testing is complete. Microvalve manifold design is complete.

3.	[redacted]	

Phase I IOCE sensor test bed is assemlbed and performance characterized with commercial lithium niobate IO technology. LLNL SOA/MZI components are assembled and characterized. Feasibility of the SOA/MZI concept is determined. Microvalve manifolds are assembled and tested.

4.	[redacted]	

Demonstration of test module incorporating all critical design components.

FY[redacted] SCHEDULED DELIVERABLES:

NUMBER	DUE DATE	COMPLETION DATE
1	[redacted]	

LLNL sends DOE/HQ Quarterly Report for October through December [redacted]

2	[redacted]	

LLNL sends DOE/HQ Quarterly Report for January through March [redacted]

3.	[redacted]	

LLNL sends DOE/HQ Quarterly Report for April through June [redacted]

4.	[redacted]	

LLNL sends DOE/HQ Quarterly Report for July through September [redacted]

5.	[redacted]	

LLNL sends DOE/HQ report on design and package engineering test data for IOCE sensor module

During FY[redacted] the following tasks will be performed:

Task 1. Develop a monolithic, chip SOA MZI chemical sensor using active/passive waveguide integration technology. Test and deliver several prototype chips. ($650K)

2.1) Fabricate laser diode, SOA and photodiode sections using CAIBE etching of a single substrate. Test individual component performance.
2.2) Fabricate passive wavegiude sections and measure loss, split ratio and extinction ratio.
2.3) Fabricate 3 dB couplers using LLNL passive waveguide technology and characterize. Integrate a single passive waveguide section with active laser diode and/or SOA.
2.4) Fabricte monolithic SOA MZI chip. Connect to CE chip using fiber. Test performance.

Task 2. Implementation of final IOCE sensor module design. Optimize source laser design. Complete system engineering tests and mechanical design characterization of final sensor module. Integrate all sub-components into final package ($850K)

Task 3. Size reduction and packaging of support electronics and system power supply ($300K)

FY98 CAPITAL $ JUSTIFICATION

Final laser technology, IO components and custom compact low energy budget data collection and signal processing electronics ($50K)

FY[redacted] SCHEDULED MILESTONES

NUMBER	DUE DATE	COMPLETION DATE

1 [redacted]
Complete final system design and design modifications.

2. [redacted]
Fabrication and testing of prototype module incorporating design changes complete.

3. [redacted]
Assembly and testing of final hardware.

4. [redacted]
Testing of sensor module under simulated field conditions complete. Operating specifications determined.

5. [redacted]
Demonstrations of selected systems for trace analysis complete

FY[redacted] SCHEDULED DELIVERABLES:

NUMBER	DUE DATE	COMPLETION DATE

1 [redacted]
LLNL sends DOE/HQ Quarterly Report for October through December [redacted]

2 [redacted]
LLNL sends DOE/HQ Quarterly Report for January through March [redacted]

3. [redacted]
LLNL sends DOE/HQ Quarterly Report for April through June [redacted]

4. [redacted]
LLNL sends DOE/HQ Quarterly Report for July through September [redacted]

5. [redacted]
LLNL send DOE/HQ report on IOCE micro sensor module integration and testing

During FY[redacted] the following tasks will be performed:

Task 1. Develop second generation SOA MZI package. Make prototypes. ($350K)

Task 2. Final modifications and optimization of IOCE sensor module package and integration of custom control microelectronics.($600K)

Task 3. Simulated field testing of completed chemical sensor module and trace analysis demonstrations. ($250K)

FY[redacted] CAPITAL $ JUSTIFICATION

Final laser technology, IO components and custom compact low energy budget data collection and signal processing electronics ($50K)

FY[redacted] SCHEDULED MILESTONES

NUMBER	DUE DATE	COMPLETION DATE
1. Task 1 complete	[redacted]	
2. Task 2 is completed.	[redacted]	
3. Demonstrations and system characerization is complete.	[redacted]	

FY[redacted] SCHEDULED DELIVERABLES:

NUMBER	DUE DATE	COMPLETION DATE
1 LLNL sends DOE/HQ Quarterly Report for October through December [redacted]	[redacted]	
2 LLNL sends DOE/HQ Quarterly Report for January through March [redacted]	[redacted]	
3. LLNL sends DOE/HQ Quarterly Report for April through June [redacted]	[redacted]	
4. LLNL sends DOE/HQ Quarterly Report for July through September [redacted]	[redacted]	
5. LLNL send DOE/HQ report on final IOCE micro sensor module design, performance characteristics and simulated field test results	[redacted]	

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8. T.Durhuss, C. Joergensen, B. Mikkelson, K.E Stubkjaer, " Monolithic Integrated Mach-Zehnder Wavelength Converter: Conversion and Transmision Experiments at 5 Gbits/s", OFC '95 Technical Digest , TuO6 ,p 75-76, [redacted]

Figure 1. The microliter water sample shown above is one thousand times larger than the typical sample volume required for chemical analysis by capillary electrophoresis (CE).

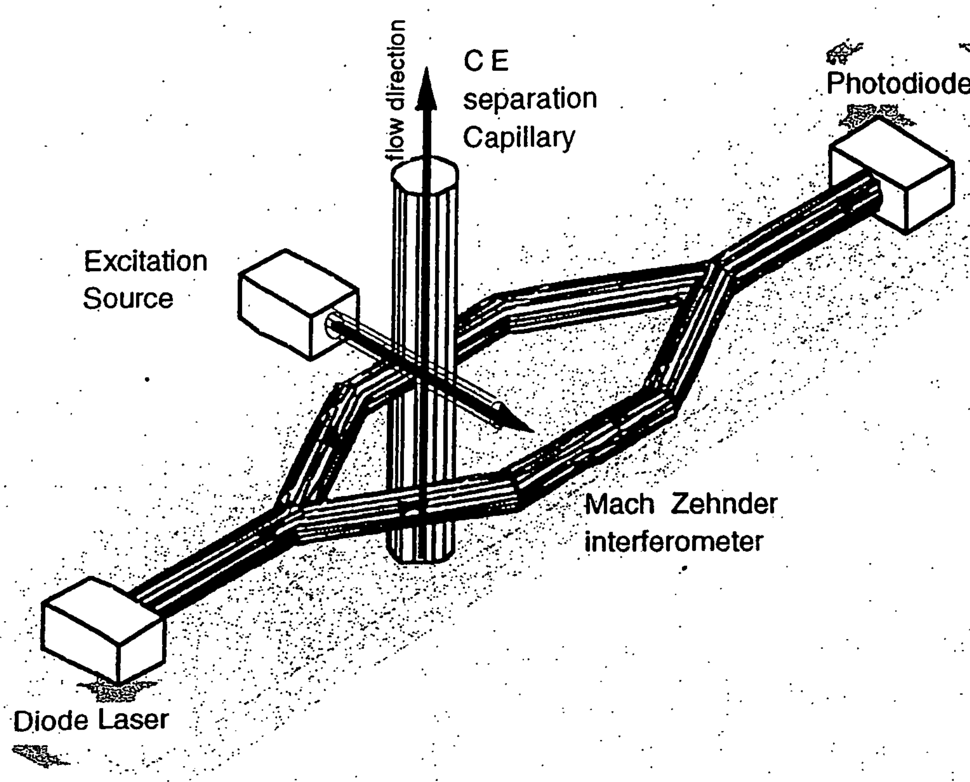

Figure 2. Conceptual diagram of the integrated optic capillary electrophoresis (IOCE) sensor module. Sample analytes are separated in the CE capillary by electrophoresis based on thier charge to mass ratio and detected by two beam interferometry. Use of a modulated excitation source increases the detection sensitivity by allowing photoinduced refractive index changes due to analyte absorption to be measured with a high signal to noise ratio.

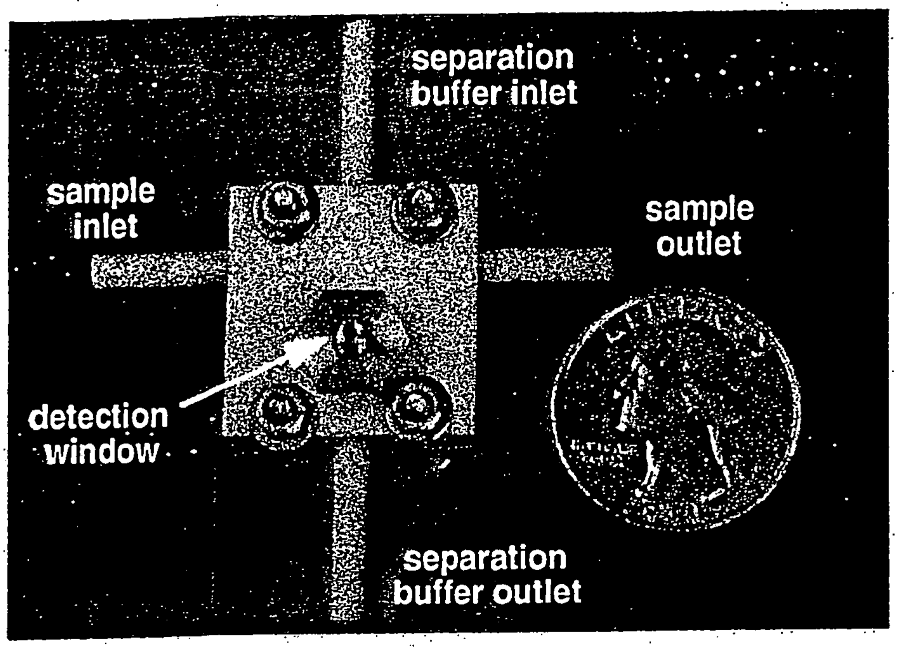

Figure 3: Ceramic planar chip CE system fabricated at LLNL for test and evaluation as part of our FY[redacted] Advanced Concepts effort.

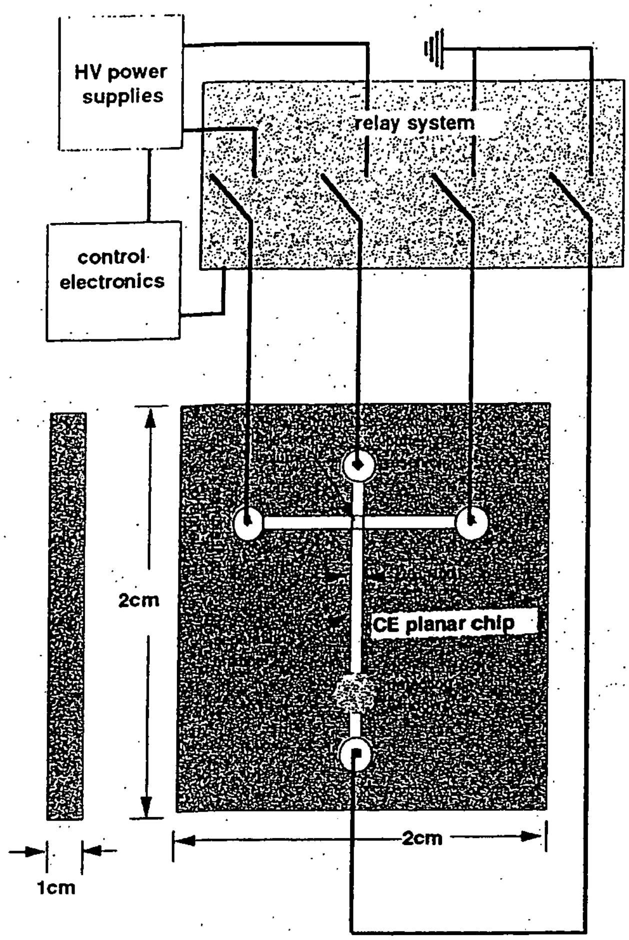

Figure 4: Schematic of capillary system micro-machined in the ceramic chip shown above. Samples are electro-kinetically injected into the separation capillary by applying a low voltage for a short period across the sample capillary. The sample is then electrophoretically separated by switching the voltage across the separation capillary.

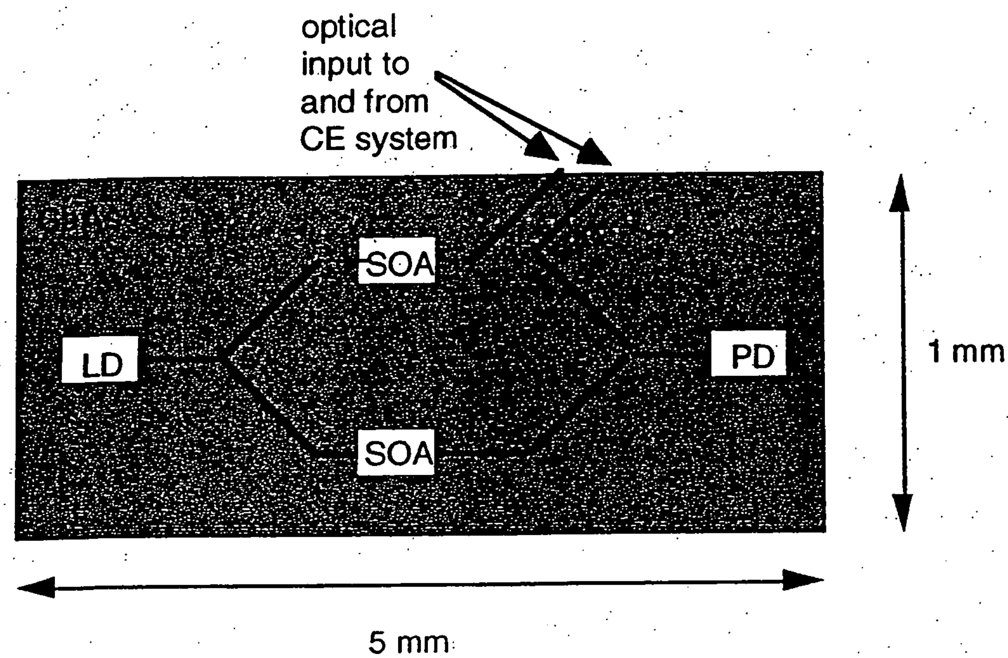

Figure 5. Schematic (not to scale) of a fully integrated Mach-Zehnder sensor using a semiconductor laser diode (LD) as the optical source, semiconductor optical amplifiers (SOAs) as optical phase shift/gain elements, passive single-mode waveguides to form the interferometer section and a semiconductor photodiode (PD) . This photonic circuit can be constructed using several existing LLNL proprietary fabrication technologies.

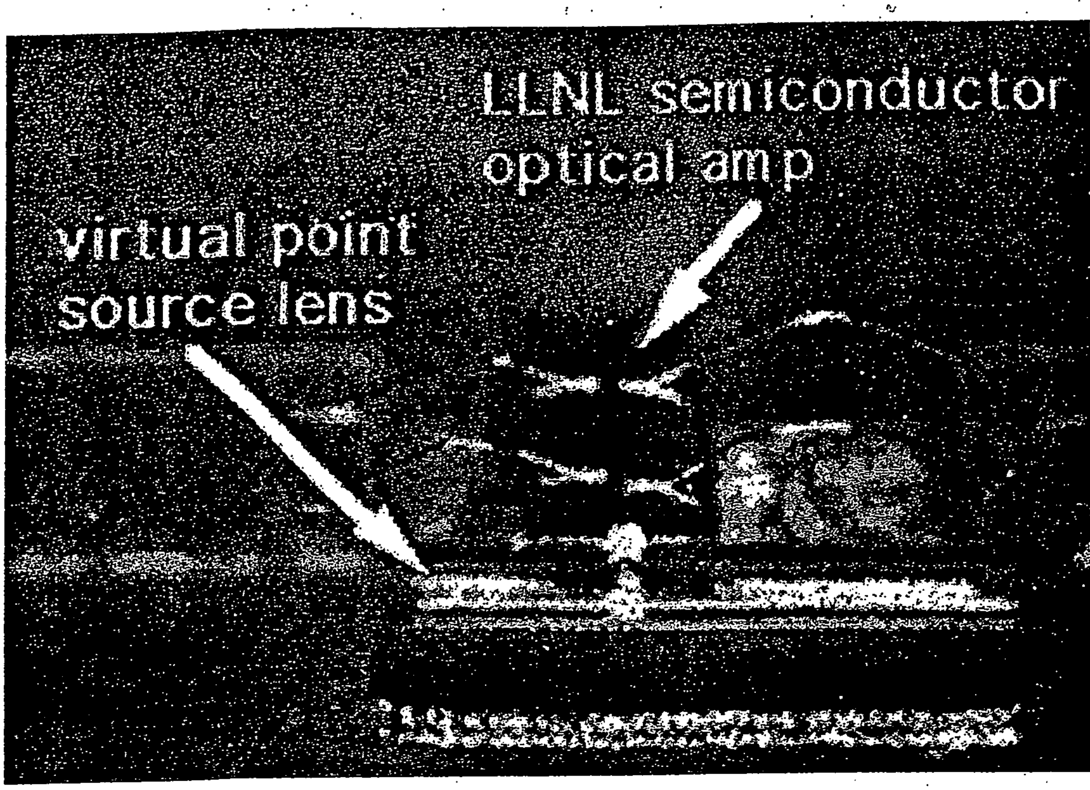

Figure 6. Example of semiconductor optical amplifiers (SOA's) fabricated and packaged at LLNL. We plan to leverage this technology in the proposed work.

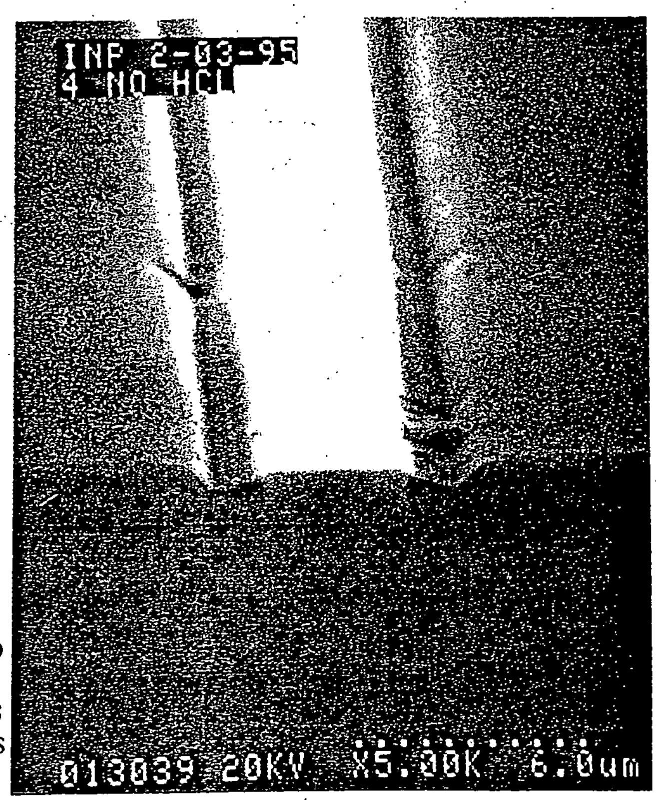

Figure 7. Scanning electron micrograph (SEM) showing the deposition of a thick oxide layer on top of an InP-based ridge SOA. In FY[redacted] we will employ this deposition process to integrate passive waveguide sections with active SOAs.

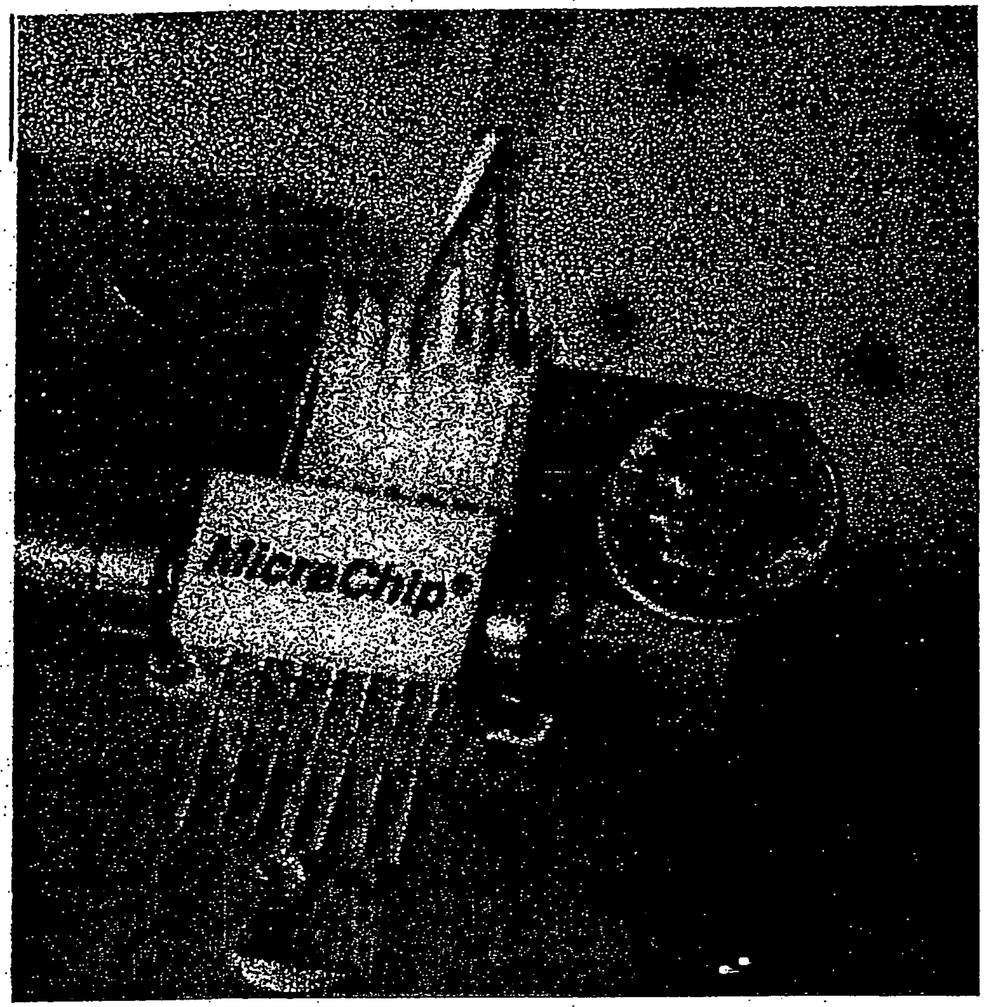

Figure 8. We plan to develop a UV excitation source suitable for the proposed IOCE sensor module based on an extention of diode pumped solid state microchip laser technology. An example of a frequency doubled commercial microchip laser is shown in the figure.

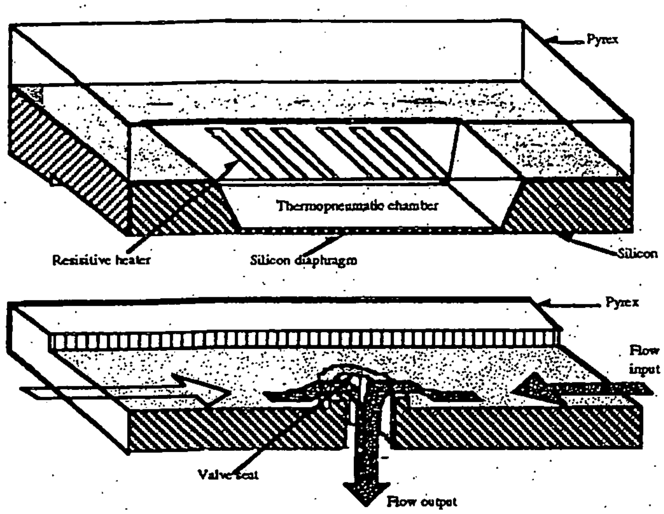

Figure 9. An exploded cross section of the thermopneumatically actuated microvalve. Heating the fluid within the chamber causes expansion, which bulges the diaphragm onto the valve seat, thereby closing the valve.

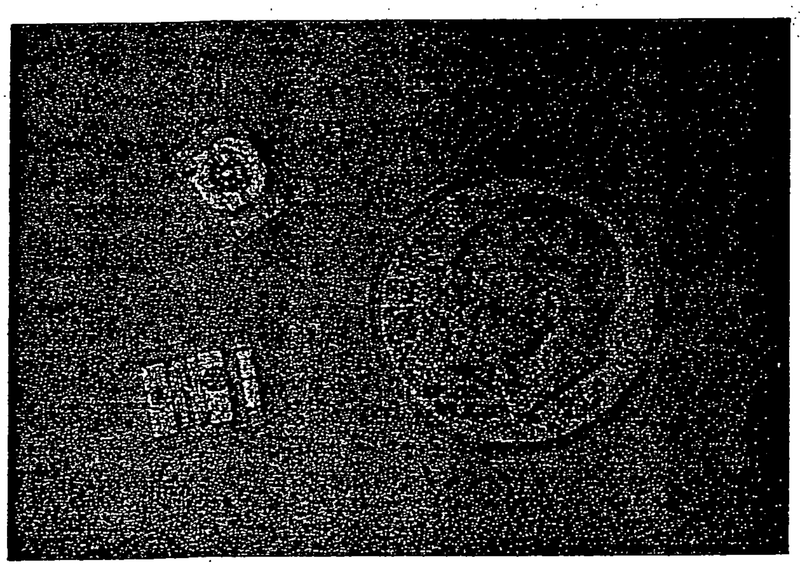

Figure 10. Redwood MicroSystems' microfabricated valve (Fluistor^{TM}). The valve measures 6x6x2mm.